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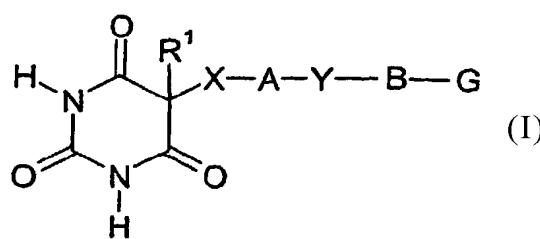
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(54) Title: PYRIMIDINE-2, 4, 6-TRIONE METALLO-PROTEINASE INHIBITORS



(57) Abstract: The present invention relates to N-substituted-heteroaryloxy-aryloxy-2, 4, 6-trione metalloproteinase inhibitors of the formula (I) wherein X, A, Y, B, G and R¹ are as defined in the specification, and to pharmaceutical compositions and methods of treating inflammation, cancer and other disorders. The compounds are matrix metalloproteinase (MMP) inhibitors.

PYRIMIDINE-2,4,6-TRIONE METALLO-PROTEINASE INHIBITORS

Background of the Invention

The present invention relates to N-substituted-heteroaryloxy-aryloxy-pyrimidine-2,4,6-trione metalloproteinase inhibitors and to pharmaceutical compositions and methods of treatment of inflammation, cancer and other disorders.

The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the class of matrix metalloproteinases (also called MMP or matrixin).

10 The MMP subfamily of enzymes currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMPs are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and 15 differentiation. In addition, the MMPs are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13 an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be overexpressed in osteoarthritic cartilage (Mitchell, *et al.*, *J. Clin. Invest.*, 97, 761 (1996)). Other MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also 20 overexpressed in osteoarthritic cartilage and inhibition of some or all of these MMPs is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis.

25 It is recognized that different combinations of MMPs are expressed in different pathological situations. As such, inhibitors with specific selectivities for individual MMPs may be preferred for individual diseases.

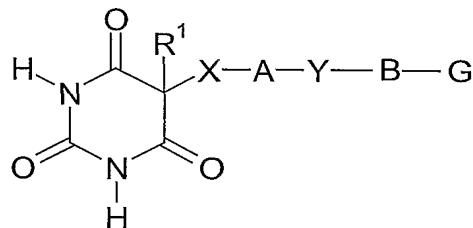
MMP inhibitors are well known in the literature. Hydroxamic acid MMP inhibitors are exemplified in European Patent Publication 606,046, published July 13, 1994. Several pyrimidine-2,4,6-trione MMP inhibitors are referred to in PCT publication WO 98/58925, published December 30, 1998. PCT publication WO 00/47565, published August 17, 2000 30 refers to certain aryl substituted pyrimidine-2,4,6-trione MMP inhibitors. United States Non-provisional application 09/635156, filed August 9, 2000 (which claims priority to United States Provisional application 60/148547 filed August 12, 1999) refers to heteroaryl substituted pyrimidine-2,4,6-trione MMP inhibitors. United States Provisional Applications entitled "Triaryl-Oxy-Aryl-Spiro-Pyrimidine-2,4,6-Trione Metalloproteinase Inhibitors"; "N-Substituted-Heteroaryloxy-Aryl-Spiro-Pyrimidine-2,4,6-Trione Metalloproteinase Inhibitors"; and "Triaryloxy-Aryloxy-Pyrimidine-2,4,6-Trione Metalloproteinase Inhibitors", all filed April 26, 35 2002, refer to certain pyrimidine-2,4,6-triones. Barbituric acids and methods for their

preparation are well known in the art, see for example Goodman and Gilman's, "The Pharmacological Basis of Therapeutics," 345-382 (Eighth Edition, McGraw Hill, 1990). Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

5 United States Non-provisional application 10/047,592, filed 23 October, 2001 (which claims priority to United States Provisional application 60/243,389 filed 26 October, 2000) refers to heteroaryl substituted pyrimidine-2,4,6-trione MMP inhibitors. United States Non-provisional application 10/032,837, filed 25 October, 2001 (which claims priority to United States Provisional application 60/243,314, filed 26 October, 2000) refers to heteroaryl
10 substituted pyrimidine-2,4,6-trione MMP inhibitors. Each of the above referenced applications refer to certain heteroaryl substituted pyrimidine-2,4,6-trione MMP inhibitors containing N-methylazetidinyl or N-methylpiperidinyl. Each of the above referenced applications is hereby incorporated by reference in its entirety.

Summary of the Invention

15 The present invention relates to compounds of the formula



wherein R¹ is selected from the group consisting of hydrogen, (R²)_{2n+1}-(C)_n- and (C₃-C₇)cycloalkyl; wherein said (C₃-C₇)cycloalkyl may be optionally substituted on any ring carbon atom able to support an additional substituent by one to two substituents independently
20 selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, R³-, R³-O-, perfluoro(C₁-C₄)alkoxy, R³-(C₁-C₄)alkyl-O-, R³-(C=O)-O-, (R³)₂N-(C=O)-O-, -NO₂, (R³)₂N-, R³-(C=O)-(NR⁴)-, R³-(SO₂)-(NR⁴)-, R³O-(C=O)-(NR⁴)-, (R³)₂N-(C=O)-(NR⁴)-, R³-S-, R³-(S=O)-, R³-(SO₂)-, (R³)₂N-(SO₂)-, -CN, R³-(C=O)-, R³-O-(C=O)- and (R³)₂N-(C=O)-;

25 n is an integer from one to five;

each R² is independently selected from the group consisting of halo, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, R³-, R³-O-, perfluoro(C₁-C₄)alkoxy, R³-(C=O)-O-, (R³)₂N-(C=O)-O-, -NO₂, (R³)₂N-, R³-(SO₂)-(NR⁴)-, (R³)₂N-(C=O)-, R³-(C=O)-(NR⁴)-, R³O-(C=O)-(NR⁴)-, (R³)₂N-(C=O)-(NR⁴)-, R³-S-, R³-(S=O)-, R³-(SO₂)-, (R³)₂N-(SO₂)-, -CN, R³-O-(C=O)-, and R³-(C=O)-;

30 wherein not more than three of said R² may be other than hydrogen and any one carbon atom of said -(C)_n- component of the R¹ can contain only one bond to a heteroatom;

wherein a carbon atom of any two R² may be taken together with the carbons to which they are attached to form a four to ten membered ring;

- each R³ is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;
- 5 wherein each R³ may be optionally substituted on any carbon atom able to support an additional substituent by one to three substituents, wherein said substituents are independently selected from the group consisting of halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, [(C₁-C₄)alkyl]₂-N-, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;
- 10 wherein each of said R³ (C₃-C₇)cycloalkyl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring;
- 15 wherein each of said R³ (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group consisting of (C₁-C₄)alkyl, (C₁-C₄)alkyl-(C=O)-, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;
- R⁴ is selected from the group consisting of hydrogen and (C₁-C₄)alkyl;
- wherein said R³ may be optionally taken together with said R⁴ to form a three to eight membered ring;
- 20 X is selected from the group consisting of -O-, >C=O, -S-, >SO₂, >S=O, >NR⁵, -CH₂-, -CH₂O-, -OCH₂-, -CH₂S-, -CH₂(S=O)-, -CH₂SO₂-, -SCH₂-, -(S=O)CH₂-, -SO₂CH₂-, -[N(R⁵)]CH₂-, -CH₂[N(R⁵)]-, -[N(R⁵)]SO₂- and -SO₂[N(R⁵)]-;
- R⁵ is selected from the group consisting of hydrogen and (C₁-C₄)alkyl;
- A is (C₆-C₁₀)aryl or (C₁-C₁₀)heteroaryl;
- 25 wherein said A (C₆-C₁₀)aryl or (C₁-C₁₀)heteroaryl may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₇)cycloalkyloxy;
- 30 Y is selected from the group consisting of a bond, -O-, -S-, >C=O, >SO₂, >S=O, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂SO₂-, -CH₂SO₂-, -SOCH₂-, -SO₂CH₂-, >NR⁶, -[N(R⁶)]CH₂-, -CH₂[N(R⁶)]-, -CH₂-, -CH=CH-, -C≡C-, -[N(R⁶)]-SO₂- and -SO₂[N(R⁶)]-;
- R⁶ is selected from the group consisting of hydrogen and (C₁-C₄)alkyl;
- B is a (C₁-C₁₀)heterocyclyl containing at least one nitrogen atom;
- 35 wherein one ring nitrogen atom of B is bonded to one carbon atom of G;
- wherein said B may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently

selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₇)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;

G is (C₁-C₆)alkyl or R⁷-(CR⁸R⁹)_p;

5 p is an integer from zero to four;

wherein said G (C₁-C₆)alkyl may be optionally substituted by one to three substituents independently selected from F, Cl, Br, CN, OH, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, -(C=O)-N[(C₁-C₄)alkyl]₂, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₇)cycloalkyloxy;

10 R⁷ is selected from the group consisting of (C₃-C₇)cycloalkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, and (C₁-C₁₀)heterocyclyl;

wherein each of said R⁷ (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂;

15 20 wherein each of said R⁷ (C₃-C₇)cycloalkyl and (C₁-C₁₀)heterocyclyl may be also optionally substituted on any of the ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring;

wherein each of said R⁷ (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O);

25 each of R⁸ and R⁹ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl;

or R⁸ and R⁹ may be optionally taken together with the carbon to which they are attached to form a 3 to 8-membered carbocyclic ring;

30 with the proviso that the group -B-G is not methylazetidinyl or methylpiperidinyl; or the pharmaceutically acceptable salts thereof.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those

35 which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate,

benzenesulfonate, para-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine (meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The compounds of this invention include all stereoisomers (e.g., cis and trans isomers) and all optical isomers of compounds of the formula I (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

The compounds of the invention may also exist in different tautomeric forms. This invention relates to all tautomers of formula I.

The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

Some compounds of formula I contain chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers, enantiomers, diastereomers and stereoisomers of the compounds of formula I and mixtures thereof. The compounds of the invention also exist in different tautomeric forms. This invention relates to all tautomers of formula I. Those skilled in the art are well aware that the pyrimidine-2,4,6-trione nucleus exists as a mixture of tautomers in solution. The various ratios of the tautomers in solid and liquid form is dependent on the various substituents on the molecule as well as the particular crystallization technique used to isolate a compound.

Unless otherwise indicated, the term "substituent" or "substituents" refers to a replacement of at least one atom of an individual member of a variable (e.g., R¹, R², and R³) of the compound of the formula I by another atom or group of atoms. For example, an (C₁-C₆)alkyl substituent may replace a hydrogen atom of the R¹ (C₆-C₁₀)aryl.

Unless otherwise indicated, the term "(C₁-C₄)alkyl" or "(C₁-C₆)alkyl", as well as the (C₁-C₄)alkyl or (C₁-C₆)alkyl component of other terms referred to herein (e.g., the "(C₁-C₆)alkyl component of (C₁-C₆)alkyl-O-), may be linear or branched (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, secondary-butyl, tertiary-butyl) hydrocarbon chain of 1 to 4, or 1 to 6, carbon atoms.

Unless otherwise indicated, the term "halo" means fluoro, chloro, bromo or iodo.

Unless otherwise indicated, the term "(C₂-C₆)alkenyl" means straight or branched hydrocarbon chain of 2 to 6 carbon atoms having at least one double bond including, but not

limited to ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, or 2-butenyl.

Unless otherwise indicated, the term "(C₂-C₆)alkynyl" is used herein to mean straight or branched hydrocarbon chain of 2 to 6 carbon atoms having one triple bond including, but not limited to, ethynyl (-C≡C-H), propynyl (-CH₂-C≡C-H or -C≡C-CH₃), or butynyl (-CH₂-CH₂-C≡C-H, or -CH₂-C≡C-CH₃, or -C≡C-CH₂CH₃).

Unless otherwise indicated, the term "(C₃-C₇)cycloalkyl" refers to a mono or bicyclic carbocyclic ring of 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and bicyclo[2.2.1]heptanyl; wherein said (C₃-C₇)cycloalkyl may optionally contain 1 or 2 double bonds including, but not limited to, cyclopentenyl, cyclohexenyl and cycloheptenyl.

Unless otherwise indicated, the term "(C₆-C₁₀)aryl" refers to an aromatic ring such as phenyl, naphthyl, tetrahydronaphthyl, or indanyl.

Unless otherwise indicated, the term "oxo" refers to a carbonyl group (i.e., =O).

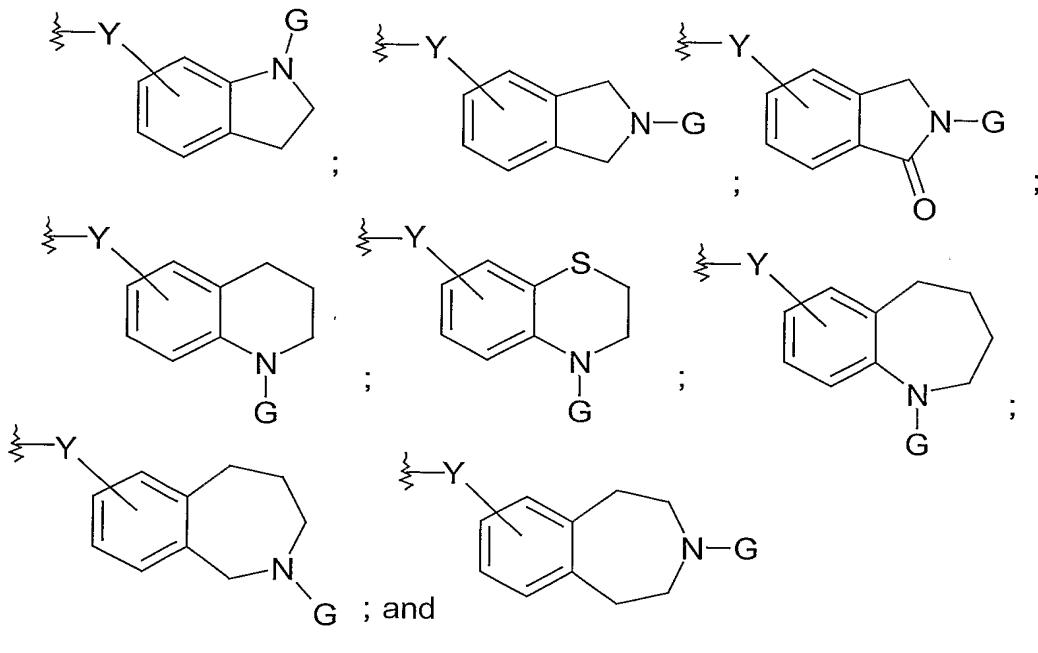
Unless otherwise indicated, the term "(C₁-C₁₀)heteroaryl" refers to aromatic or multicyclic rings wherein at least one ring is aromatic, wherein said aromatic or multicyclic rings contain one or more heteroatoms selected from the group consisting of O, S and N. Examples of (C₁-C₁₀)heteroaryl include, but are not limited to, benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl. Unless otherwise indicated, the foregoing (C₁-C₁₀)heteroaryl may be C-attached or N-attached where such is possible.

Unless otherwise indicated, such as in the above definition B, the term "(C₁-C₁₀)heterocyclyl" refers to a ring containing 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of N, O and S. Examples of (C₁-C₁₀)heterocyclyl include, but not limited to, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]-heptanyl, azetidinyl, dihydrofuran, dihydropyran, dihydrothienyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydroazepinyl, hexahydropyrimidine, imidazolidinyl, imidazolinyl, isoxazolidinyl, morpholinyl, oxetanyl, oxazolidinyl, piperazinyl, piperidinyl, 2H-pyran, 4H-pyran, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, quinolizinyl, tetrahydrofuran, tetrahydropyran, 1,2,3,6-tetrahydropyridinyl, tetrahydrothienyl, tetrahydrothiopyran, thiomorpholinyl, thioxanyl or trithianyl. Unless otherwise indicated, the foregoing (C₁-C₁₀)heterocyclyl may be C-attached or N-attached where such is possible. For example, piperidinyl may be piperidin-1-yl (N-attached) or piperidin-4-yl (C-attached).

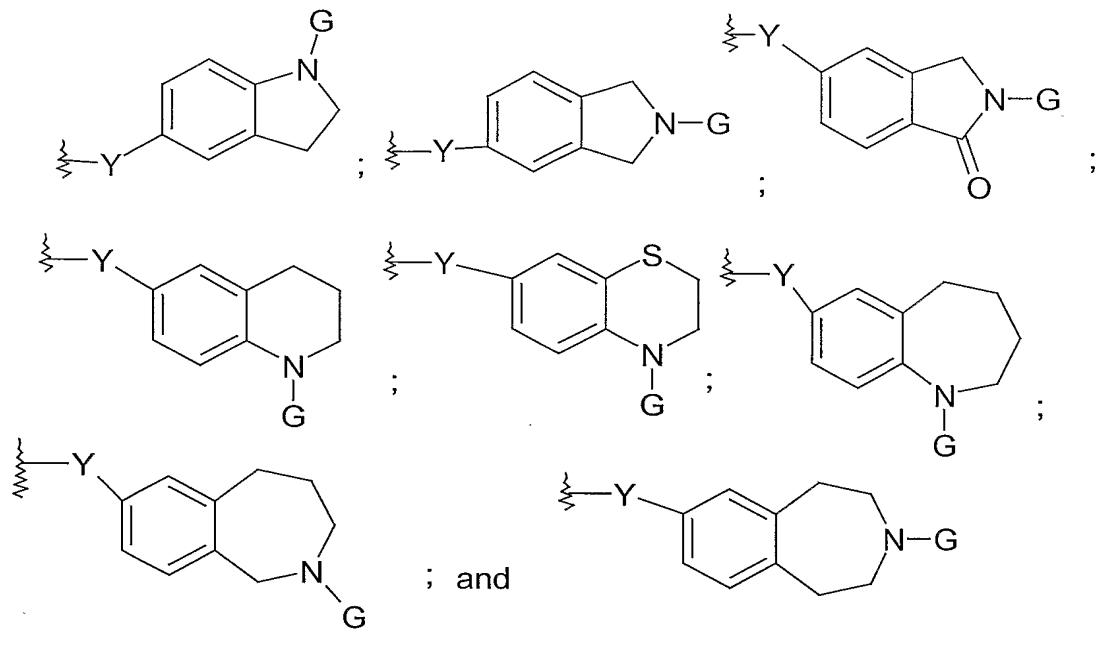
In another embodiment of the invention, B is a monocyclic saturated (5- to 7-membered)-heterocyclic ring containing at least one nitrogen atom selected from the group consisting of pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, and piperazinyl; wherein said B may optionally be substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₇)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

In another embodiment of the invention, B is a monocyclic saturated (5- to 7-membered)-heterocyclic ring containing at least one ring nitrogen atom fused to an aromatic six membered ring, such as indolinyl, or isoindolinyl; wherein said B may optionally be substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, (C_3 - C_7)cycloalkyloxy, (C_6 - C_{10})aryl, (C_3 - C_7)cycloalkyl, (C_1 - C_{10})heteroaryl and (C_1 - C_{10})heterocyclyl.

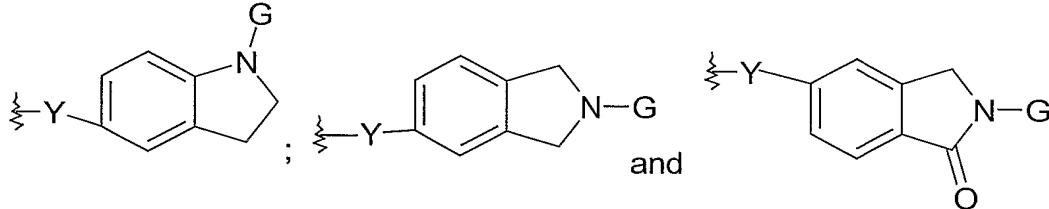
In another embodiment of the invention, the group -Y-B-G has the formulae selected from the group consisting of



preferably selected from the group consisting of



more preferably selected from the group consisting of



In another embodiment of the invention, B is a monocyclic partially saturated
 5 (5- to 7-membered)-ring containing at least one nitrogen atom, such as 2-pyrrolyl, 3-pyrrolyl, imidazolyl, 2-imidazolyl, or 2-pyrazolyl; wherein said B may optionally be substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₇)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.
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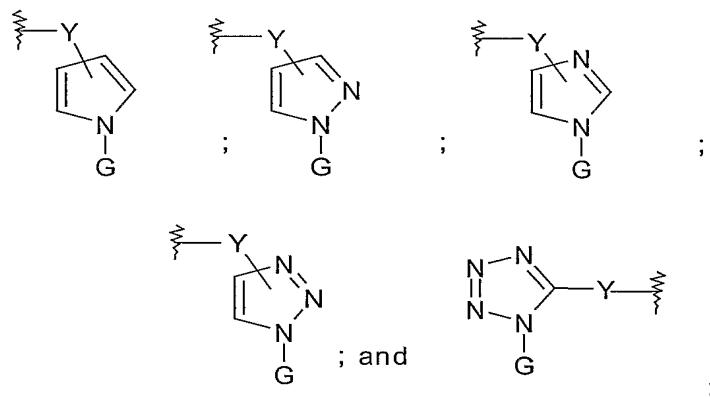
In another embodiment of the invention, B is a partially saturated (5- to 7-membered)-heterocyclic ring containing at least one nitrogen atom fused to an aromatic six membered ring, such as 3H-indolyl; wherein said B may optionally be substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₇)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.
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In another embodiment of the invention, B is a monocyclic aromatic (5- to 6-membered)-heterocyclic ring containing at least one nitrogen atom, such as tetrazolyl,

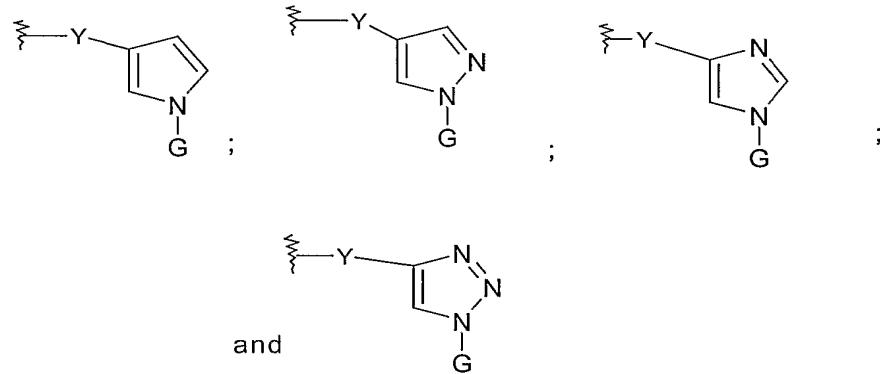
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pyrrolyl, imidazolyl, pyrazolyl, or triazolyl; wherein said B may optionally be substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₇)cycloalkyloxy, 5 (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

In another embodiment of the invention, the group -Y-B-G has the formulae selected from the group consisting of



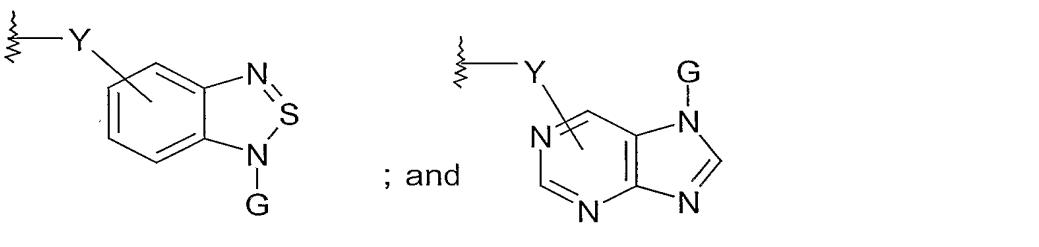
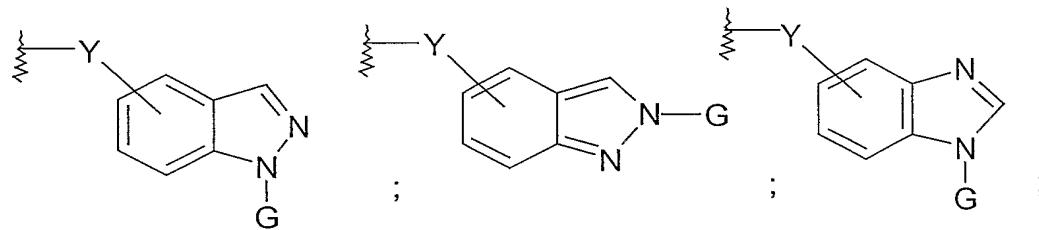
preferably selected from the group consisting of



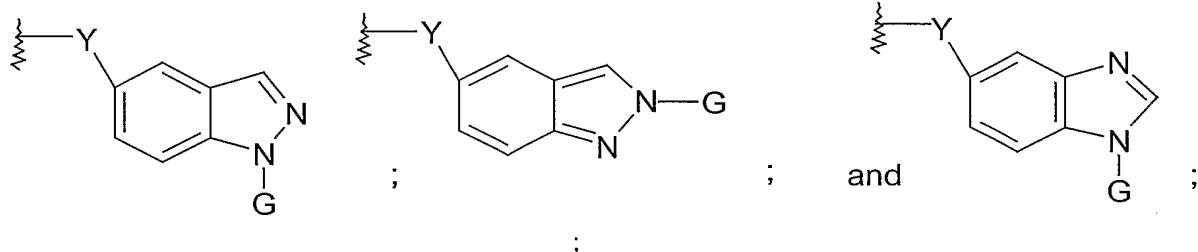
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In another embodiment of the invention, B is an aromatic (5- to 6-membered)-ring containing at least one nitrogen atom fused to an aromatic six membered ring, such as indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, and purinyl; wherein said B may optionally be substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₇)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; and wherein the group -Y-B-G has the formulae selected from the group consisting of

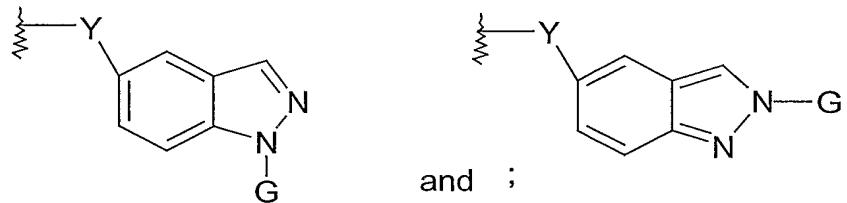
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preferably selected from the group consisting of



5 more preferably selected from the group consisting of



In another embodiment of the invention, A is (C_1-C_{10})heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thietyl, triazinyl and triazolyl, wherein said (C_1-C_{10})heteroaryl is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy and (C_3-C_7)cycloalkyloxy; preferably A is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl,

oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; more preferably A is pyrazinyl, pyridazinyl, pyridyl or pyrimidinyl; most preferably A is pyridinyl. Within each of the aforesaid embodiments, Y is selected from the group consisting of a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- and -CH₂O-; preferably Y is -O-, -OCH₂- or -CH₂O-; more preferably Y is -O-.

5 In another embodiment of each of the above embodiments of the invention, A is (C₆-C₁₀)aryl, such as phenyl or naphthyl, preferably A is phenyl. Within each of the aforesaid embodiments, Y is selected from the group consisting of a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- and -CH₂O-; preferably Y is -O-, -OCH₂- or -CH₂O-; more preferably Y is -O-.

10 In another embodiment of the invention, A is substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₇)cycloalkyloxy.

15 In another embodiment of the invention, both A and B are substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₇)cycloalkyloxy; preferably selected from the group consisting of F, Cl, CN, methyl, and methoxy.

In another preferred embodiment of the invention, either A or B is unsubstituted.

In another preferred embodiment of the invention, both A and B are unsubstituted.

20 In another embodiment of the invention, G is (C₁-C₆)alkyl; wherein said (C₁-C₆)alkyl may be optionally substituted by one to three substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₇)cycloalkyloxy; preferably selected from F, Cl, Br, CN, OH, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₇)cycloalkyloxy;

25 more preferably selected from F, Cl, CN, OH, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, and (C₃-C₇)cycloalkyloxy; most preferably selected from F, CN, OH, perfluoromethyl, methoxy, ethoxy, propoxy, cyclopentyloxy, and cyclohexyloxy.

30 In another embodiment of the invention, G is optionally substituted (C₁-C₆)alkyl, such as methyl, ethyl, isopropyl, isobutyl, 2-hydroxyethyl, 2-ethoxyethyl, or 2,2-dimethyl-2-hydroxyethyl.

In another embodiment of the invention, G is (C₃-C₇)cycloalkyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂; and wherein said (C₃-C₇)cycloalkyl may be optionally substituted on any ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring.

In another embodiment of the invention, G is (C_6-C_{10})aryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NH₂, -NO₂, 5 (C_1-C_4)alkyl-NH-, [(C_1-C_4)alkyl]₂-N-, (C_3-C_7)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, and -(C=O)-N[(C_1-C_4)alkyl]₂; preferably G is phenyl 10 optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, and (C_3-C_7)cycloalkyloxy; more preferably G is phenyl 15 optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one substituent per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy.

In another embodiment of the invention, G is unsubstituted (C_6 - C_{10})aryl; preferably G is unsubstituted phenyl.

In another embodiment of the invention, G is (C_1 - C_{10})heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxaliny, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl; wherein said (C_1 - C_{10})heteroaryl is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, (C_1 - C_4)alkoxy(C_1 - C_4)alkyl, -NH₂, -NO₂, (C_1 - C_4)alkyl-NH-, [(C_1 - C_4)alkyl]₂-N-, (C_3 - C_7)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1 - C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1 - C_4)alkyl, and -(C=O)-N[(C_1 - C_4)alkyl]₂; preferably G is (C_1 - C_{10})heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, (C_1 - C_4)alkoxy(C_1 - C_4)alkyl and (C_3 - C_7)cycloalkyloxy; more preferably G is (C_1 - C_{10})heteroaryl selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy; most preferably G is pyridinyl or pyridazinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy;

atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from F, Cl, CN, methyl, methoxy.

In a preferred embodiment of the invention, G is pyridinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy.

In another preferred embodiment of the invention, G is pyridazinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy.

In another preferred embodiment of the invention, G is pyrazinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy.

In another embodiment of the invention, G is unsubstituted (C_1-C_{10})heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl; preferably G is unsubstituted pyridinyl, pyridazinyl or pyrazinyl.

In another embodiment of the invention, G is (C_1-C_{10})heterocyclyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NH₂, -NO₂, (C_1-C_4)alkyl-NH-, [(C_1-C_4)alkyl]₂-N-, (C_3-C_7)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, and -(C=O)-N[(C_1-C_4)alkyl]₂; and wherein said (C_1-C_{10})heterocyclyl may be optionally substituted on any ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring.

In another embodiment of the invention, G is R⁷-(CR⁸R⁹)_p-; wherein p is an integer from one to four, preferably from one to two; and wherein each of R⁸ or R⁹ is independently hydrogen, methyl, ethyl, propyl, or isopropyl.

In another embodiment of the invention, G is R⁷-(CR⁸R⁹)_p; wherein p is an integer from one to four, preferably from one to two; and wherein R⁸ and R⁹ are taken together with the carbon to which they are attached to form a 3 to 8-membered carbocyclic ring selected

from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, and cyclohexenyl.

In another embodiment of the invention, G is $(C_3-C_7)cycloalkyl-(CR^8R^9)_p$; wherein p is an integer from one to four, preferably from one to two; said $(C_3-C_7)cycloalkyl$ is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, $(C_1-C_4)alkyl$, $(C_1-C_4)perfluoroalkyl$, $(C_1-C_4)perfluoroalkoxy$, $(C_1-C_4)alkoxy$, $(C_1-C_4)alkoxy(C_1-C_4)alkyl$, $-NH_2$, $-NO_2$, $(C_1-C_4)alkyl-NH-$, $[(C_1-C_4)alkyl]_2-N-$, $(C_3-C_7)cycloalkyloxy$, $-(C=O)-OH$, $-(C=O)-O-(C_1-C_4)alkyl$, $-(C=O)-NH_2$, $-(C=O)-NH-(C_1-C_4)alkyl$, and $-(C=O)-N[(C_1-C_4)alkyl]_2$; wherein said $(C_3-C_7)cycloalkyl$ may be optionally substituted on any ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring; and wherein each of R^8 and R^9 is independently hydrogen.

In another embodiment of the invention, G is $(C_6-C_{10})aryl-(CR^8R^9)_p$; wherein p is an integer from one to four, preferably from one to two; wherein said $(C_6-C_{10})aryl$ is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, $(C_1-C_4)alkyl$, $(C_1-C_4)perfluoroalkyl$, $(C_1-C_4)perfluoroalkoxy$, $(C_1-C_4)alkoxy$, $(C_1-C_4)alkoxy(C_1-C_4)alkyl$, $-NH_2$, $-NO_2$, $(C_1-C_4)alkyl-NH-$, $[(C_1-C_4)alkyl]_2-N-$, $(C_3-C_7)cycloalkyloxy$, $-(C=O)-OH$, $-(C=O)-O-(C_1-C_4)alkyl$, $-(C=O)-NH_2$, $-(C=O)-NH-(C_1-C_4)alkyl$, and $-(C=O)-N[(C_1-C_4)alkyl]_2$; and wherein each of R^8 and R^9 is independently hydrogen.

In another embodiment of the invention, G is $(C_1-C_{10})heteroaryl-(CR^8R^9)_p$; wherein p is an integer from one to four, preferably from one to two; wherein said $(C_1-C_{10})heteroaryl$ is selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl; wherein said $(C_1-C_{10})heteroaryl$ is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, $(C_1-C_4)alkyl$, $(C_1-C_4)perfluoroalkyl$, $(C_1-C_4)perfluoroalkoxy$, $(C_1-C_4)alkoxy$, $(C_1-C_4)alkoxy(C_1-C_4)alkyl$, $-NH_2$, $-NO_2$, $(C_1-C_4)alkyl-NH-$, $[(C_1-C_4)alkyl]_2-N-$, $(C_3-C_7)cycloalkyloxy$, $-(C=O)-OH$, $-(C=O)-O-(C_1-C_4)alkyl$, $-(C=O)-NH_2$, $-(C=O)-NH-(C_1-C_4)alkyl$, and $-(C=O)-N[(C_1-C_4)alkyl]_2$; preferably said $(C_1-C_{10})heteroaryl$ is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, $(C_1-C_4)alkyl$,

(C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₇)cycloalkyloxy; more preferably said (C₁-C₁₀)heteroaryl is selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring

5 independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy.

In another embodiment of the invention, G is (C₁-C₁₀)heterocyclyl-(CR⁸R⁹)_p; wherein p is an integer from one to four, preferably from one to two; wherein said (C₁-C₁₀)heterocyclyl is optionally substituted on any of the ring carbon atoms capable of supporting an additional 10 substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂; and wherein said (C₁-C₁₀)heterocyclyl may be optionally substituted on any ring carbon atoms 15 capable of supporting two additional substituents with one to two oxo groups per ring; and wherein each of R⁸ and R⁹ is independently hydrogen.

Another embodiment of the invention includes those compounds of formula I wherein X is -O-, -S-, >SO₂, >S=O, >NR⁵, or -CH₂-; preferably wherein X is -O- or >NR⁵; more preferably wherein X is -O-.

20 Another embodiment of the invention includes those compounds of formula I wherein Y is a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- or -CH₂O-; preferably wherein Y is -O-, -OCH₂- or -CH₂O-; more preferably wherein Y is -O-.

Another embodiment of the invention includes those compounds of formula I wherein X is >C=O; and wherein Y is a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- or -CH₂O-, preferably wherein 25 Y is -O-, -OCH₂- or -CH₂O-, most preferably wherein Y is -O-.

Preferred compounds of the invention include those wherein X is -O-, -OCH₂-, -CH₂O-, more preferably wherein X is -O-; and wherein Y is a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- or -CH₂O-, more preferably wherein Y is -O-, -OCH₂- or -CH₂O-, most preferably wherein Y is -O-.

Other embodiments of the invention include those compounds of formula I wherein X is -S-, >SO₂, >S=O, -SCH₂-, -CH₂S-, -(S=O)CH₂-, -CH₂(S=O)-, -CH₂SO₂- or -SO₂CH₂-, more 30 preferably wherein Y is a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- or -CH₂O-, more preferably wherein Y is -O-, -OCH₂- or -CH₂O-, most preferably wherein Y is -O-.

Other embodiments of the invention include those compounds of formula I wherein X is >NR⁵, -CH₂[N(R⁵)]- or -[N(R⁵)]CH₂-, more preferably wherein Y is a bond, -O-, -S-, -CH₂-, >SO₂, 35 -OCH₂- or -CH₂O-, more preferably wherein Y is -O-, -OCH₂- or -CH₂O-, most preferably wherein Y is -O-.

Other embodiments of the invention include those compounds of formula I wherein X is $-[N(R^5)]SO_2-$ or $-SO_2[N(R^5)]-$, more preferably wherein Y is a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- or -CH₂O-, more preferably wherein Y is -O-, -OCH₂-, most preferably wherein Y is -O-.

Most preferred embodiment of the invention includes those compounds of formula I
5 wherein X and Y are each -O-.

Other embodiments of the invention include those compounds of formula I wherein R¹ is (C₃-C₇)cycloalkyl wherein said (C₃-C₇)cycloalkyl may be also optionally substituted on any ring carbon atom capable of supporting an additional substituent by one to two substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, R³-, R³-O-, perfluoro(C₁-C₄)alkoxy, R³-(C₁-C₄)alkyl-O-, R³-(C=O)-O-, -NO₂, (R³)₂N-, R³-(C=O)-(NR⁴)-, R³-S-, R³-(S=O)-, R³-(SO₂)-, R³-(SO₂)-(NR⁴)-, R³-NH-(SO₂)-, (R³)₂N-(SO₂)-, -CN, R³-(C=O)-, R³-O-(C=O)- and (R³)₂N-(C=O)-.

Other embodiments of the invention include those compounds of formula I wherein R¹ is (R²)_{2n+1}-(C)_n- and n is an integer from one to five; each R² is independently selected from the
15 group consisting of halo, R³-, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, R³-O-, perfluoro(C₁-C₄)alkoxy, R³-(C=O)-O-, (R³)₂N-(C=O)-O-, -NO₂, (R³)₂N-, R³-(SO₂)-(NR⁴)-, R³-(C=O)-(NR⁴)-, R³O-(C=O)-(NR⁴)-, (R³)₂N-(C=O)-(NR⁴)-, R³-S-, R³-(S=O)-, R³-(SO₂)-, (R³)₂N-(SO₂)-, -CN, R³-(C=O)-, R³-O-(C=O)- and (R³)₂N-(C=O)-; wherein not more than three of said R²
20 substituents may be other than hydrogen and any one carbon atom of said -(C)_n- group can contain only one bond to a heteroatom; each R³ is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocycl; wherein each R³ may be optionally substituted on any carbon atom capable of supporting an additional substituent by one to three substituents independently selected from the group consisting of halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy,
25 (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocycl; and wherein said R³ group may be optionally taken together with R⁴ to form a three to eight membered ring.

Other embodiments of the invention include those compounds of formula I wherein R¹ is (R²)_{2n+1}-(C)_n-, n is an integer from one to five; at least one R² is independently selected from the
30 group consisting of R³-, R³-O-, R³-(C=O)-O-, R³-S-, R³-(S=O)-, R³-(SO₂)-, (R³)₂N-, R³-(SO₂)-(NR⁴)-, R³-NH-(SO₂)-, (R³)₂N-(SO₂)-, R³-(C=O)-(NR⁴)-, R³-O-(C=O)- and R³-(C=O)-; and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein each R³ (C₁-C₄)alkyl may be optionally substituted by one to three substituents independently selected from the group consisting of halo, hydroxy, amino,
35 -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocycl; wherein said R³ group may be optionally taken together with R⁴ to form a three to eight membered ring.

Other embodiments of the invention include those compounds of formula I wherein R¹ is (R²)_{2n+1}-(C)_n-, n is an integer from one to five; and each R² is independently selected from the group consisting of hydrogen, halo, (C₁-C₄)alkyl, R³- and R³-O-.

Other embodiments of the invention include those compounds of formula I wherein R¹ is 5 (R²)_{2n+1}-(C)_n-, n is one to five, preferably one or two;

R² is independently selected from the group consisting of R³-, R³-O-, (R³)₂N-, R³-S-, R³-(S=O)-, R³-(SO₂)-, R³-(SO₂)-(NR⁴)-, R³-NH-(SO₂)-, (R³)₂N-(SO₂)-, R³-(C=O)-(NR⁴)-, R³-(C=O)-O-, R³-O-(C=O)- and R³-(C=O)-; and

each R³ is independently selected from the group consisting of hydrogen, 10 (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;

wherein each R³ (C₁-C₄)alkyl may be optionally substituted by one to three substituents independently selected from the group consisting of halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;

15 wherein each R³ (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any ring carbon atom capable of supporting an additional substituent by one to three substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, 20 (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

Other embodiments of the invention include those compounds of formula I wherein R¹ is (R²)_{2n+1}-(C)_n-, n is one to four, preferably one or two; wherein each R² is independently selected from the group consisting of R³- and R³-O-; wherein each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein each R³ (C₁-C₄)alkyl may be 25 optionally substituted by one to three substituents independently selected from the group consisting of (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

Other embodiments of the invention include those compounds of formula I wherein R¹ is (R²)_{2n+1}-(C)_n-, n is one to four, preferably one or two; each R² is independently selected from the group consisting of R³- and R³-O-; wherein any four of said R³ are hydrogen and any one of said 30 R³ is (C₁-C₄)alkyl; wherein each R³ (C₁-C₄)alkyl may be optionally substituted by one to three substituents independently selected from the group consisting of (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

Other embodiments of the invention include those compounds of formula I wherein n is 35 one to three; and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein each R³ (C₁-C₄)alkyl may be optionally substituted by one to three substituents independently selected from the group consisting of halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

Other embodiments of the invention include those compounds of formula I wherein n is one to three; and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein at least one R³ (C₁-C₄)alkyl group is substituted by halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

5 Other embodiments of the invention include those compounds of formula I wherein n is one or two; and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein at least one R³ (C₁-C₄)alkyl group is substituted by (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, or [(C₁-C₄)alkyl]₂-N-.

10 Other embodiments of the invention include those compounds of formula I wherein at least one of said R³ groups is (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl or (C₁-C₁₀)heterocyclyl; wherein each of said R³ (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl or (C₁-C₁₀)heterocyclyl groups may be optionally substituted on any ring carbon atom capable of supporting an additional substituent by one to three substituents independently selected

15 from the group consisting of halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

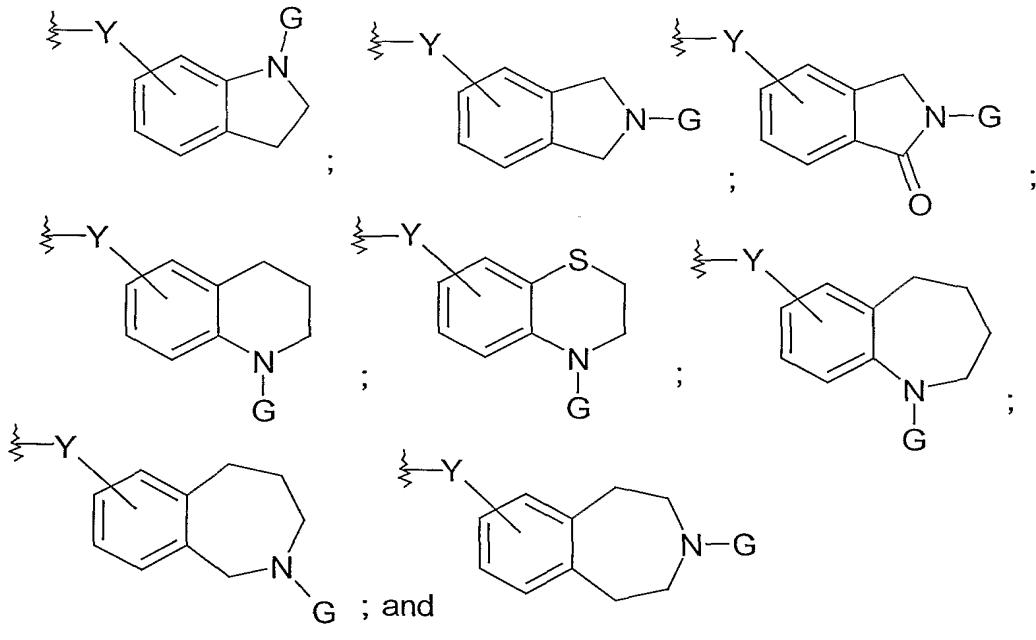
More preferred R¹ is (C₁-C₄)alkoxy(C₁-C₄)alkyl, most preferably R¹ is ethoxyethyl or methoxyethyl.

20 More preferred compounds of the invention include compounds of formula I, wherein X is -O-, Y is -O-; R¹ is (R²)_{2n+1}-(C)_n-, n is one; each R² is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein at least one R² (C₁-C₄)alkyl group is substituted by (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH- or [(C₁-C₄)alkyl]₂-N-.

25 Other preferred compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; B is optionally substituted indazolyl; G is optionally substituted (C₁-C₆)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; R¹ is (R²)_{2n+1}-(C)_n-, n is one; each R² is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, R³- and R³-O-; and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein one R³ (C₁-C₄)alkyl group is optionally substituted by (C₁-C₄)alkoxy; preferably wherein the R³ (C₁-C₄)alkyl group is unsubstituted.

30 Other compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; B is optionally substituted indolinyl; G is optionally substituted (C₁-C₆)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; R¹ is (R²)_{2n+1}-(C)_n-, n is one; each R² is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, R³- and R³-O-; and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein one R³ (C₁-C₄)alkyl group is optionally substituted by (C₁-C₄)alkoxy; preferably wherein the R³ (C₁-C₄)alkyl group is unsubstituted.

Other compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; the group -Y-B-G has the formulae selected from the group consisting of



5 wherein G is (C_1-C_6)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; R^1 is $(R^2)_{2n+1}-(C)_n-$, n is one; each R^2 is independently selected from the group consisting of hydrogen, (C_1-C_4)alkyl, R^3- and R^3-O- and each R^3 is independently selected from the group consisting of hydrogen and (C_1-C_4)alkyl; wherein one R^3 (C_1-C_4)alkyl group is optionally substituted by (C_1-C_4)alkoxy; preferably wherein the R^3 (C_1-C_4)alkyl group is unsubstituted.

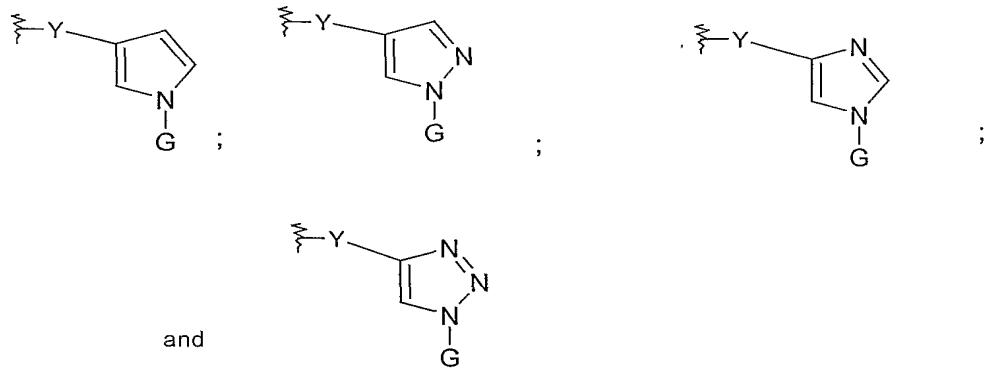
10 Other compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; B is optionally substituted 2-pyrrolinyl, 3-pyrrolinyl, imidazolyl, 2-imidazolinyl, 2-pyrazolinyl, or 3H-indolyl; G is optionally substituted (C_1-C_6)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; R^1 is $(R^2)_{2n+1}-(C)_n-$, n is one; each R^2 is independently selected from the group consisting of hydrogen, (C_1-C_4)alkyl, R^3- and R^3-O- and each R^3 is independently selected from the group consisting of hydrogen and (C_1-C_4)alkyl; wherein one R^3 (C_1-C_4)alkyl group is optionally substituted by (C_1-C_4)alkoxy; preferably wherein the R^3 (C_1-C_4)alkyl group is unsubstituted.

15 Other compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; B is tetrazolyl, pyrrolyl, imidazolyl, pyrazolyl, or triazolyl; G is optionally substituted (C_1-C_6)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; and R^1 is $(R^2)_{2n+1}-(C)_n-$, n is one; each R^2 is independently selected from the group consisting of hydrogen, (C_1-C_4)alkyl, R^3- and R^3-O- and each R^3 is independently selected from the group consisting of

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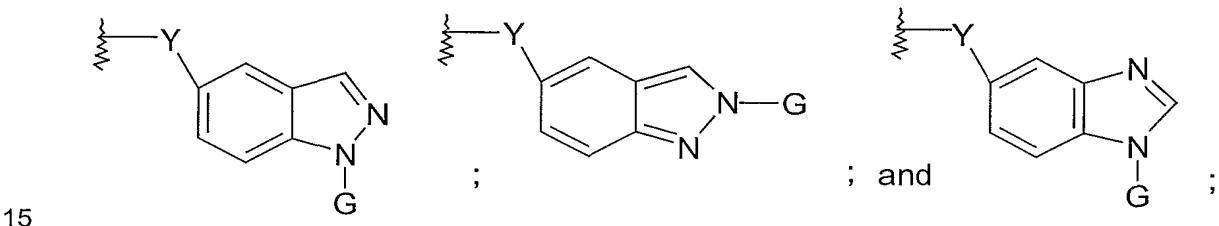
hydrogen and (C₁-C₄)alkyl; wherein one R³ (C₁-C₄)alkyl group is optionally substituted by (C₁-C₄)alkoxy; preferably wherein the R³ (C₁-C₄)alkyl group is unsubstituted.

Other compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; the group -Y-B-G has the formulae selected from the group consisting of



G is optionally substituted (C₁-C₆)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; and R¹ is (R²)_{2n+1}-(C)_n, n is one; each R² is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, R³- and R³-O- and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein one R³ (C₁-C₄)alkyl group is optionally substituted by (C₁-C₄)alkoxy; preferably wherein the R³ (C₁-C₄)alkyl group is unsubstituted.

Other preferred compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; the group -Y-B-G has the formulae selected from the group consisting of



G is optionally substituted (C₁-C₆)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; and R¹ is (R²)_{2n+1}-(C)_n, n is one; each R² is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, R³- and R³-O- and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein one R³ (C₁-C₄)alkyl group is optionally substituted by (C₁-C₄)alkoxy; preferably wherein the R³ (C₁-C₄)alkyl group is unsubstituted.

Most preferred compounds of the invention include those wherein X is -O-; A is optionally substituted phenyl; Y is -O-; B is 1H-indazolyl, 2H-indazolyl, or benzimidazolyl; G is optionally substituted (C₁-C₆)alkyl, phenyl, pyridyl, pyrazinyl, or pyridazinyl; and R¹ is (R²)_{2n+1}-(C)_n, n is one; each R² is independently selected from the group consisting of hydrogen,

(C₁-C₄)alkyl, R³- and R³-O- and each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein one R³ (C₁-C₄)alkyl group is optionally substituted by (C₁-C₄)alkoxy; preferably wherein the R³ (C₁-C₄)alkyl group is unsubstituted.

Other compounds of the invention are selected from the group consisting of:

5 [4-(1-Isopropyl-1H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-pyridin-2-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-phenyl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

10 5-(2-Methoxy-ethyl)-5-{4-[1-(5-nitro-pyridin-2-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-{4-[1-(5-Amino-pyridin-2-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

15 5-(2-Methoxy-ethyl)-5-[4-(1-methyl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-[4-(1-Ethyl-1H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-{4-[1-(2-Hydroxy-ethyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

20 5-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-{4-[1-(2-Ethoxy-ethyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

25 3-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-propionitrile;

5-[4-(1-Isobutyl-1H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

30 5-(2-Methoxy-ethyl)-5-[4-(1-pyrimidin-2-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-pyrazin-2-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

35 5-(2-Methoxy-ethyl)-5-[4-(1-pyridin-3-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-pyridin-4-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[1-(6-Chloro-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-pyridazin-3-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[1-(6-methyl-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-pyrimidin-5-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[1-(5-Fluoro-pyridin-2-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-pyrimidin-4-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[1-(6-methoxy-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-{4-[1-(3-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

6-{5-[4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-nicotinonitrile;

4-{5-[4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-benzonitrile;

5-{4-[1-(5-Chloro-pyridin-2-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-{4-[1-(2-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

3-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-benzonitrile;

5-{4-[1-(3-Fluoro-pyridin-2-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[1-(2-methyl-pyridin-4-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-{4-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[1-(2-methoxy-pyridin-4-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-(2-Ethoxy-ethyl)-5-{4-[1-(4-fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-nicotinonitrile;

5-{4-[1-(2-Dimethylamino-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

2-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-benzonitrile;

5-(2-Methoxy-ethyl)-5-{4-[1-(tetrahydro-pyran-4-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-{6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yloxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-[4-(2-Isopropyl-2H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

4-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-2-yl)-benzonitrile;

5-(2-Methoxy-ethyl)-5-[4-(2-pyridin-2-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-phenyl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-methyl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-[4-(2-Ethyl-2H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-{4-[2-(2-Hydroxy-2-methyl-propyl)-2H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-{4-[2-(2-Ethoxy-ethyl)-2H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-[4-(2-Isobutyl-2H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-pyrazin-2-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-pyridin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[2-(6-Chloro-pyridin-3-yl)-2H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-pyridazin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-pyridin-4-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[2-(6-methyl-pyridin-3-yl)-2H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-{4-[2-(5-Chloro-pyridin-2-yl)-2H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-pyrimidin-4-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5 5-{4-[2-(5-Fluoro-pyridin-2-yl)-2H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione; and

6-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-2-yl)-nicotinonitrile; or

the pharmaceutically acceptable salts thereof.

10 Preferred compounds of the invention are selected from the group consisting of:

5-(2-Methoxy-ethyl)-5-[4-(1-pyridin-3-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

15 5-(2-Methoxy-ethyl)-5-[4-(2-pyridin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[1-(6-Chloro-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(1-pyridazin-3-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

20 5-(2-Methoxy-ethyl)-5-[4-(2-pyridazin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[1-(6-methyl-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

25 5-(2-Methoxy-ethyl)-5-{4-[2-(6-methyl-pyridin-3-yl)-2H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-pyrimidin-4-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

30 5-{4-[2-(5-Fluoro-pyridin-2-yl)-2H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[1-(6-methoxy-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-{4-[1-(3-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

35 6-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-2-yl)-nicotinonitrile;

6-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-nicotinonitrile;

3-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-benzonitrile; and

5-(2-Ethoxy-ethyl)-5-{4-[1-(4-fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione; or

5 the pharmaceutically acceptable salts thereof.

The present invention also relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers and other diseases characterized by metalloproteinase activity in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

15 The present invention also relates to a pharmaceutical composition for the treatment of a condition which may be treated by the inhibition of matrix metalloproteinases in a mammal, including a human, comprising an amount of a compound of formula I effective in such treatment and a pharmaceutically acceptable carrier.

20 The present invention also relates to a method for the inhibition of matrix metalloproteinases in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I.

25 The present invention also relates to a method for treating a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers and other diseases characterized by matrix metalloproteinase activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

30 The present invention also relates to a method for the inhibition of matrix metalloproteinases or other metalloproteinases involved in matrix degradation, in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

35 The present inventors have also discovered that it is possible to identify inhibitors of formula I with differential metalloprotease activity (preferably MMP-13 inhibitory activity). One group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1. The compounds of the invention also possess selectivity over a related group of enzymes known as reprolysin, such as TACE

and aggrecanase. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1 and MMP-14. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1 and 12.

5 Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1, 12 and 14. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1, 2, 3, 7, 9 and 14. Most preferred compounds of the invention selectively inhibit MMP-13 preferentially over any two or more of

10 MMP-1, 2, 3, 7, 9, 12 and 14 and mammalian reproxysins.

The present invention also relates to a method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably substituted pyrimidine-2,4,6-trione exhibits: i) a ratio of MMP-1 IC₅₀ / MMP-13 IC₅₀ of about 50, and ii) a ratio of MMP-14 IC₅₀ / MMP-13 IC₅₀ of about 50; wherein said MMP-1 IC₅₀ is measured by a recombinant MMP-1 assay; wherein each of said MMP-13 IC₅₀ is measured by a recombinant MMP-13 assay; and wherein said MMP-14 IC₅₀ is measured by a recombinant MMP-14 assay.

20 The present invention also relates to a method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably substituted pyrimidine-2,4,6-trione additionally exhibits iii) a ratio of MMP-12 IC₅₀ / MMP-13 IC₅₀ of about 50; wherein said MMP-12 IC₅₀ is measured by a recombinant MMP-12 assay; and wherein said MMP-13 IC₅₀ is measured by a recombinant MMP-13 assay.

The present invention also relates to a method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably substituted pyrimidine-2,4,6-trione additionally exhibits iv) a ratio of MMP-2 IC₅₀ / MMP-13 IC₅₀ of about 50, and v) a ratio of MMP-3 IC₅₀ / MMP-13 IC₅₀ of about 50; vi) a ratio of MMP-7 IC₅₀ / MMP-13 IC₅₀ of about 50, and vii) a ratio of MMP-9 IC₅₀ / MMP-13 IC₅₀ of about 50; wherein said MMP-2 IC₅₀ is measured by a recombinant MMP-2 assay; wherein said MMP-3 IC₅₀ is measured by a recombinant MMP-3 assay; wherein said MMP-7 IC₅₀ is measured by a recombinant MMP-7 assay; wherein said MMP-9 IC₅₀ is measured by a recombinant MMP-9 assay; and each of said MMP-13 IC₅₀ is measured by a recombinant MMP-13 assay.

The present invention also relates to a method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably substituted pyrimidine-2,4,6-trione exhibits an MMP-13 IC₅₀ of less than about 100nM, preferably of less than about 50 nM; more preferably of less than about 20 nM.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act 10 of treating, as "treating" is defined immediately above.

"Connective tissue disorders" as used herein refers to disorders such as degenerative cartilage loss following traumatic joint injury, osteoarthritis, osteoporosis, Paget's disease, loosening of artificial joint implants, periodontal disease and gingivitis.

"Destruction of articular cartilage" as used herein refers to connective tissue disorders 15 resulting in articular cartilage destruction, preferably joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, or juvenile rheumatoid arthritis, more preferably osteoarthritis.

"Inflammatory disorders" as used herein refers to disorders such as rheumatoid 20 arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibromyalgia and cachexia.

"Immunology/allergy disorders" as used herein refers to disorders such as organ transplant toxicity, allergic reactions, allergic contact hypersensitivity, autoimmune disorders such as those disorders associated with granulomatous inflammation/tissue remodeling (such as asthma), immunosuppression and sarcoid.

25 "Infectious diseases," including those mediated by viruses, bacteria, fungi or mycobacterial infection, as used herein refers to disorders such as septic arthritis, AIDS, fever; Prion diseases, myasthenia gravis, Malaria, sepsis, hemodynamic shock and septic shock.

"Respiratory diseases" as used herein refers to disorders such as chronic obstructive 30 pulmonary disease (including emphysema), acute respiratory distress syndrome, asthma, hyperoxic alveolar injury and idiopathic pulmonary fibrosis and other fibrotic lung diseases.

"Cardiovascular diseases" as used herein refers to disorders such as atherosclerosis including atherosclerotic plaque rupture; aortic aneurysm including abdominal aortic aneurysm and brain aortic aneurysm; congestive heart failure; myocardial and cerebral infarction; stroke; 35 cerebral ischemia; coagulation and acute phase response; left ventricular dilation; post ischemic reperfusion injury; angiofibromas; hemangiomas; and restenosis.

"Eye diseases" as used herein refers to disorders such as aberrant angiogenesis, ocular angiogenesis, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular

tumors, corneal graft rejection, corneal injury, neovascular glaucoma, corneal ulceration, corneal scarring, macular degeneration (including "Age Related Macular Degeneration (ARMD) including both wet and dry forms), proliferative vitreoretinopathy and retinopathy of prematurity.

5 "Metabolic diseases" as used herein refers to disorders such as diabetes (including non-insulin dependent diabetes mellitus, diabetic retinopathy, insulin resistance, diabetic ulceration).

10 "Central Nervous System" (CNS) disorders as used herein refers to disorders such as head trauma, spinal cord injury, Inflammatory diseases of the central nervous system, neuro-degenerative disorders (acute and chronic), Alzheimer's disease, demyelinating diseases of the nervous system, Huntington's disease, Parkinson's disease, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, migraine, depression and anorexia.

15 "Liver/Kidney diseases" as used herein refers to disorders such as nephrotic syndromes such as glomerulonephritis and glomerular disease of the kidney, proteinuria, cirrhosis of the liver and interstitial nephritis.

"Reproductive Health disorders" as used herein refers to disorders such as endometriosis, contraception (male/female), dysmenorrhea, dysfunctional uterine bleeding, premature rupture of fetal membranes and abortifacient.

20 "Gastric disorders" as used herein refers to disorders such as colonic anastomosis and gastric ulcers.

25 "Skin disorders" as used herein refers to disorders such as skin aging, pressure sores, psoriasis, eczema, dermatitis, radiation damage, tissue ulceration, decubital ulcers, epidermolysis bullosa, abnormal wound healing (topical and oral formulations), burns and scleritis.

30 "Cancers" as used herein refers to disorders such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostate cancer, tumor invasion, tumor growth tumor metastasis, cancers of the oral cavity and pharynx (lip, tongue, mouth, pharynx), esophagus, stomach, small intestine, large intestine, rectum, liver and biliary passages, pancreas, larynx, lung, bone, connective tissue, skin, cervix uteri, corpus endometrium, ovary, testis, bladder, kidney and other urinary tissues, eye brain and central nervous system, thyroid and other endocrine gland, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma and hematopoietic malignancies including leukemias and lymphomas including lymphocytic, granulocytic and monocytic.

35 The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that may be incorporated into

compounds of the invention include isotopes of hydrogen, carbon, nitrogen, -O-, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that may be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprodysin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy, sulfonamide or carboxylic groups may be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amido, amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters, which are covalently, bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include dimers of compounds of formula I.

One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF- α inhibitors such as anti-TNF monoclonal antibodies

(such as infliximab, D2E7 and CDP-870) and TNF receptor immunoglobulin molecules (such as etanercept), ICE inhibitors, MEKK1 inhibitors, COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib and etoricoxib; low dose methotrexate, lefunimide, steroids, glucosamines, chondrosamines/ sulfates, gabapentin, A-agonists, IL-1 process and release 5 inhibitors, IL-1 receptor antagonists such as Kineret®, CCR-1 antagonists, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) 10 such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, paracoxib, etoricoxib and rofecoxib, analgesics, steroids, glucosamines, chondrosamines/ sulfates, gabapentin, A-agonists, IL-1 process and release 15 inhibitors, CCR-1 antagonists, LTD-4, LTB-4 and 5-LO inhibitors, p38 kinase inhibitors and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, 20 daunomycin, cis-platinum, etoposide, paclitaxel, docetaxel and alkaloids, such as vincristine and antimetabolites such as methotrexate.

The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers (such as amlodipine and nifedipine), lipid lowering agents such as statins (such as lovastatin, atorvastatin, pravastatin and 25 simvastatin), adrenergics such as doxazosin and terazosin; fibrates, beta-blockers, ACE inhibitors (such as captopril, lisinopril, fosinopril, enalapril and quinapril), Angiotensin-2 receptor antagonists such as losartan and irbesartan; nitrates, CCB's, diuretics such as digitalis and platelet aggregation inhibitors. The compounds of the present invention may also be used in combination with plaque rupture preventive agents such as statins, zithromax, 30 NSAIDs including aspirin, heparin, urarfarin, abciximab, TPA and platelet Inhibitors. The compounds of the present invention may also be used in combination with stroke treatment agents such as NIF, NHEI's and CCRIR antagonists.

The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as 35 deprenyl, carbadopa, L-dopa, dopamine receptor agonists such as ropinirole, pergolide and pramipexole; MAOB inhibitors such as selegiline and rasagiline, catechol-O-methyltransferase inhibitors such as tolcapone, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists,

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Nicotine agonists, NK-1 inhibitors, dopamine agonists and inhibitors of neuronal nitric oxide synthase) and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with
5 osteoporosis agents such as roloxitene, droloxitene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

The compounds of the present invention may also be used in combination with agents
for the treatment of respiratory diseases such as PDE-IV inhibitors, steroidals such as
10 fluticasone, triamcinolone, budesonide, budesonide and beclomethasone, anticholinergics
such as ipratropium, sympathomimetics such as salmeterol, albuterol and Xopenex,
decongestants such as fexofenadine, loratadine and cetirizine; leukotriene antagonists such
as zafirlukast and motilukast; and mast cell stabilizers such as zileuton.

The compounds of the present invention may also be used in combination with agents
for the treatment of skin disorders such as tretinoin, isotretinoin, steroids such as cortisone
15 and mometasone, antibiotics such as tetracycline, antifungals such as clotrimazole,
miconazole and fluconazole and PDE-IV inhibitors.

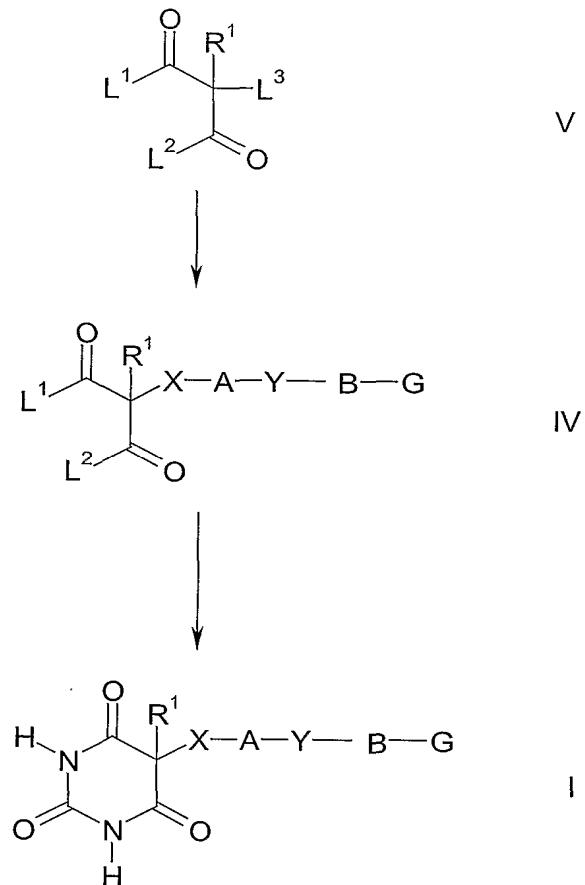
The compounds of the present invention may also be used in combination with agents
for the treatment of diabetes such as insulin, including human or humanized insulin and
inhaled insulin, aldose reductase inhibitors, sorbitol dehydrogenase inhibitors, antidiabetic
20 agents such as biguanides such as metformin; glitazones, glycosidase inhibitors such as
acarbose, sulfonylureas such as glimepiride and glipizide; and thiazolidinediones such as
pioglitazone, rosiglitazone and troglitazone. Preferred combinations are useful for treating the
side effects of diabetes such as retinopathy, nephropathy and neuropathy, preferably
retinopathy.

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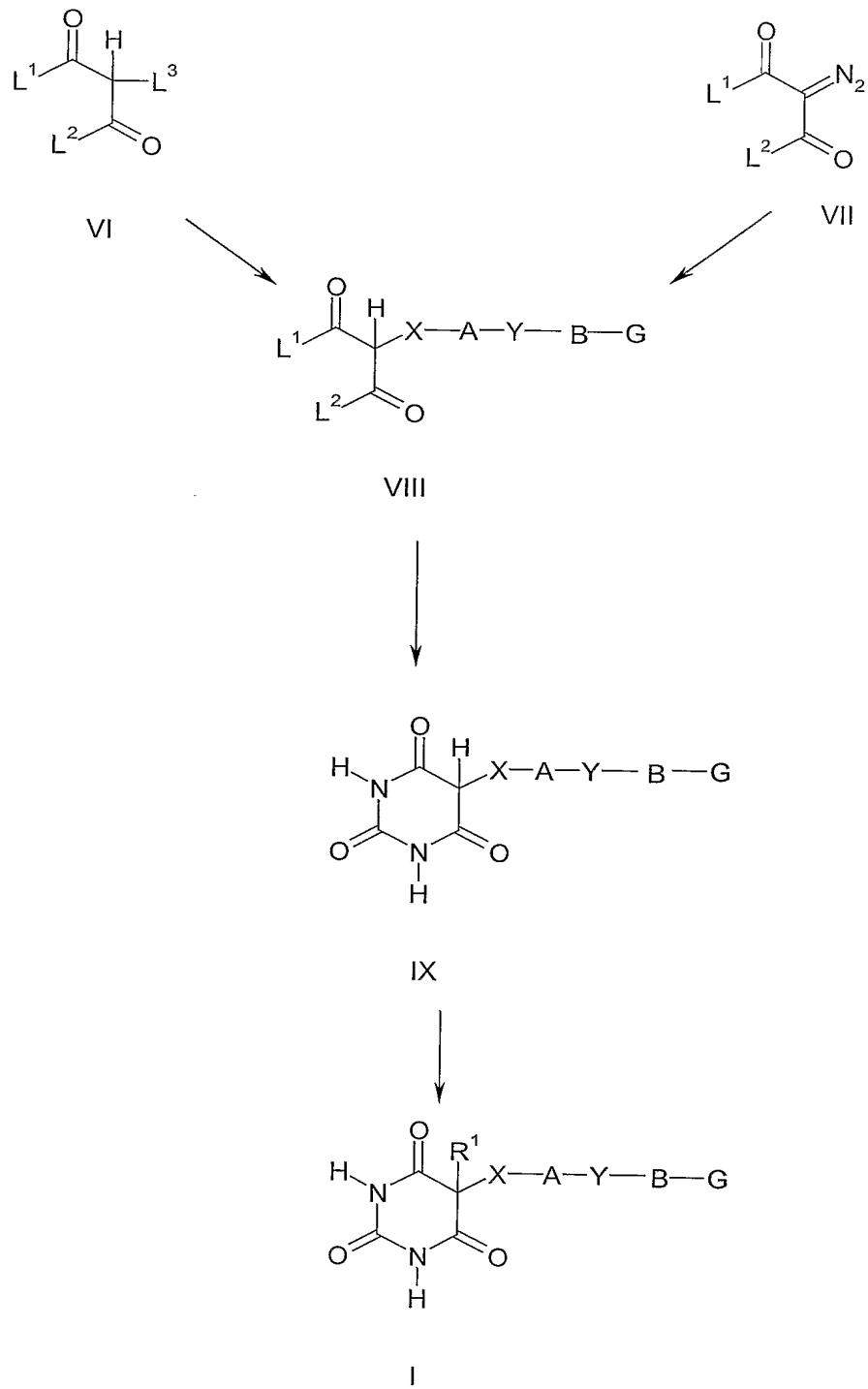
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the
present invention. Unless otherwise indicated each of X, A, Y, B, G, R¹, R², R³, R⁴, R⁵, R⁶, R⁷,
R⁸, and R⁹ in the reaction Schemes and the discussion that follows is defined as above.

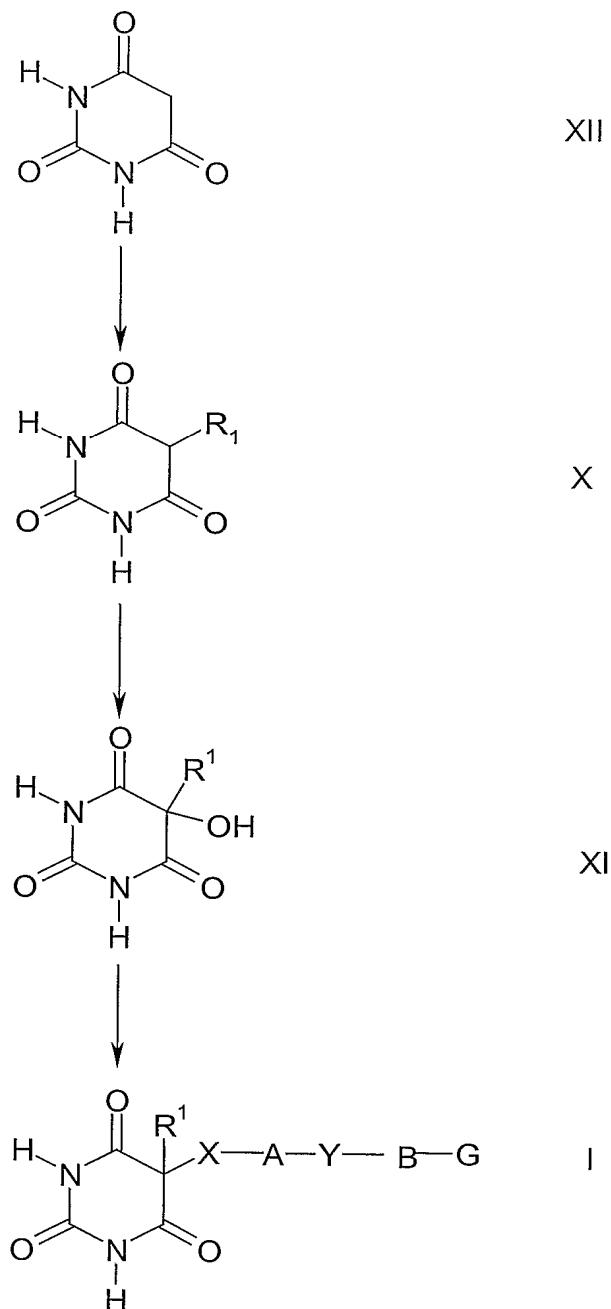
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SCHEME 1

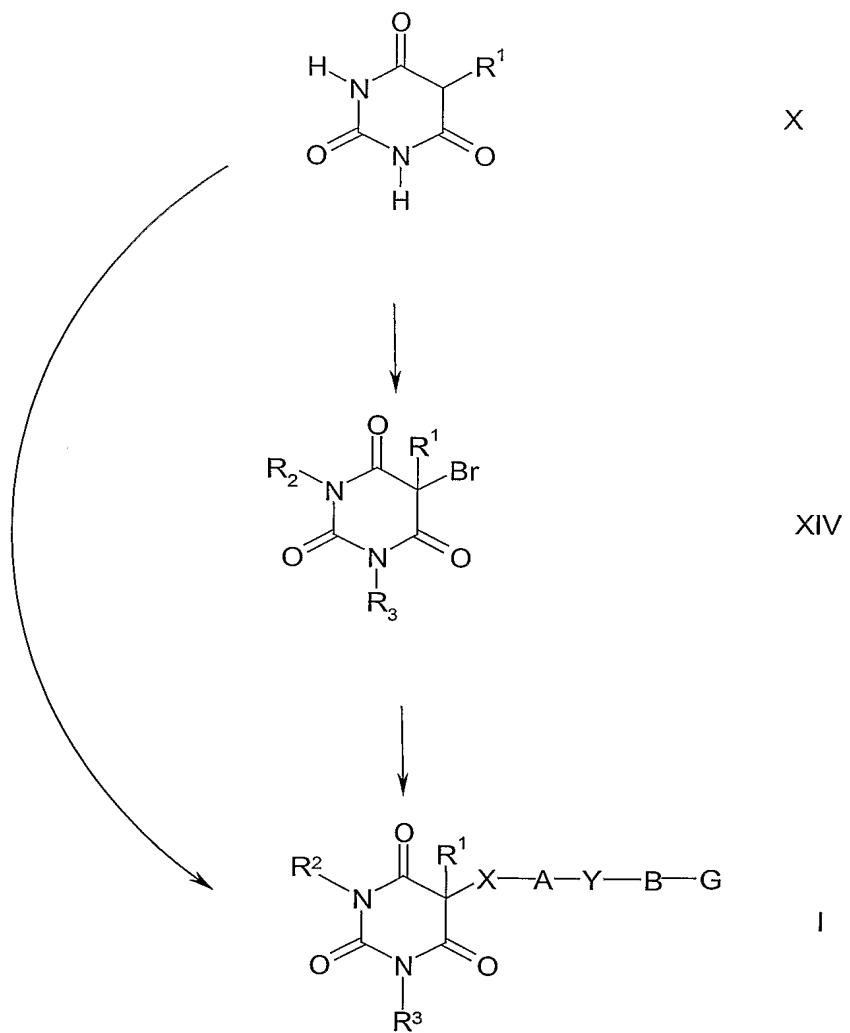
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SCHEME 2

-34-

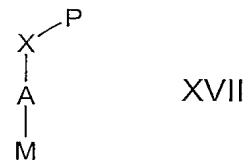
SCHEME 3

-35-

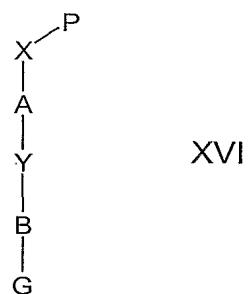
SCHEME 4

-36-

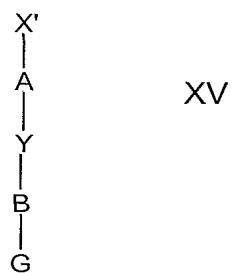
SCHEME 5



XVII

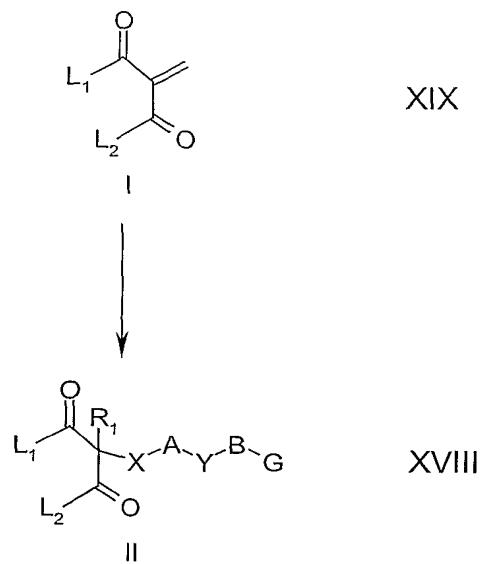


XVI

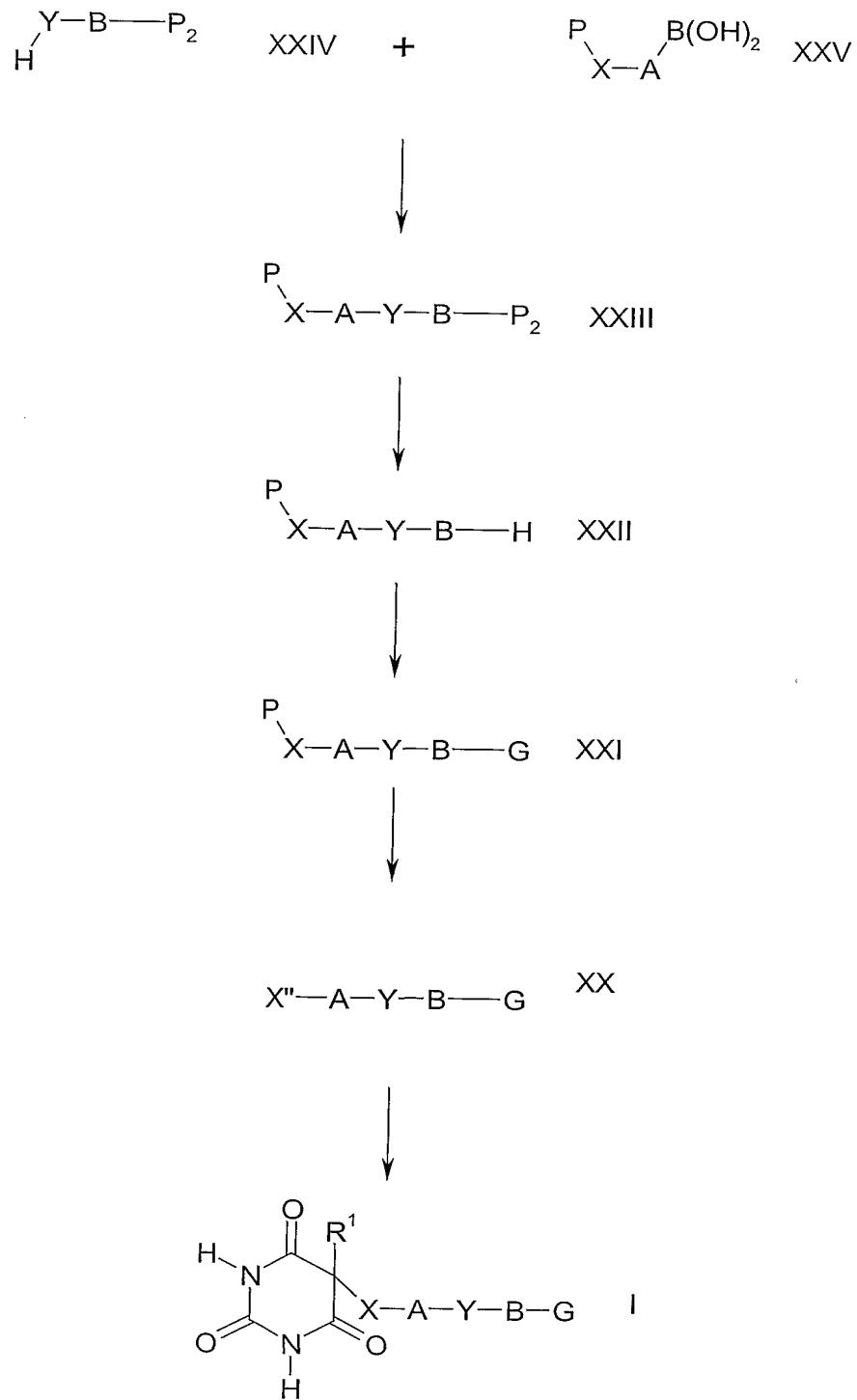


XV

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SCHEME 6

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SCHEME 7

Scheme 1 refers to the preparation of compounds of the formula I in a two step synthesis from compounds of the formula V. Referring to Scheme 1, a compound of the formula I may be prepared by reacting a compound of the formula IV, wherein L¹ and L² are leaving groups such as methoxy, ethoxy, benzyloxy or chloro, preferably ethoxy, with a urea of the formula III (H₂NCONH₂) in the presence of a strong base in a polar solvent. Suitable bases include sodium methoxide, sodium ethoxide and magnesium methoxide, preferably sodium ethoxide. Suitable solvents include alcohols (such as ethanol) or tetrahydrofuran, preferably absolute ethanol. The aforesaid reaction may be conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 65°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

The compound of formula IV is prepared by reacting a compound of formula V, wherein L³ is a leaving group such as halo, p-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), preferably halo, most preferably chloro or bromo, with a compound of the formula II (i.e., compounds of the formula H-X-A-Y-B-G) in the presence of a base in a polar solvent. Suitable solvents include dimethylformamide (DMF), alcohols (such as ethanol) or tetrahydrofuran, preferably ethanol. The aforesaid reaction may be conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 65°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

The compounds of the formula V may be made by methods well known in the art such as those described in PCT Patent Publication WO 98/58925 or reviewed in The Organic Chemistry of Drug Synthesis, D. Lednicer and L. A. Mitscher, Volume 1, pages 167 to 277 and references therein. Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

Compounds of the formula III are commercially available or may be made by methods well known to those skilled in the art.

The compounds of formula II (H-X-A-Y-B-G), are commercially available or may be made by methods well known to those skilled in the art or may be made by the methods of Scheme 5.

Scheme 2 refers to an alternate preparation of compounds of the formula I in a three-step synthesis from compounds of the formula VI or VII. Referring to Scheme 2, a compound of the formula I is prepared by reacting a compound of the formula IX with a suitable base and a suitable R¹ introducing agent in the presence of a solvent. Suitable bases include sodium hydride, potassium carbonate, sodium carbonate, triethylamine, pyridine or triethanolamine; preferably sodium hydride. Suitable R¹ introducing agents include compounds of the formula R¹L⁴ wherein L⁴ is halo, p-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), preferably halo, more preferably chloro or bromo; or alkylating agents such as Eshenmoser's Salts, epoxides or suitably substituted electrophilic aziridines. Suitable solvents depend upon the base used but

may be chosen from N,N-dimethylformamide, tetrahydrofuran, acetonitrile or water. The aforesaid reaction may be conducted at a temperature of about 0°C to about 30°C, preferably about 20°C to about 25°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

5 A compound of the formula IX may be prepared by reacting a compound of the formula VIII with a urea of the formula III (H_2NCONH_2) in the presence of a strong base in a polar solvent. Suitable bases include sodium methoxide, sodium ethoxide and magnesium methoxide; preferably sodium ethoxide. Suitable solvents include alcohols (such as ethanol) or tetrahydrofuran, preferably absolute ethanol. The aforesaid reaction may be conducted at a
10 temperature of about 20°C to about 90°C, preferably about 50°C to about 65°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

A compound of the formula VIII may be prepared by reacting a compound of the formula VI, , wherein L¹ and L² are leaving groups such as methoxy, ethoxy, benzyloxy or chloro, preferably ethoxy, and wherein L³ is a leaving group such as halo, p-tolylsulfonyloxy (OTs) or
15 methylsulfonyloxy (OMs), preferably halo, most preferably chloro, with a compound of the formula II (i.e., compounds of the formula H-X-A-Y-B-G) in the presence of a base in a polar solvent. Suitable bases include sodium methoxide, sodium ethoxide, potassium carbonate and sodium hydride; preferably sodium ethoxide. Suitable solvents include dimethylformamide, alcohols (such as ethanol) or tetrahydrofuran, preferably ethanol. The aforesaid reaction may be
20 conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 70°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours, preferably about 3 hours. Reactions of this type are further illustrated by the method of J. B. Niederl and R. T. Roth, J. Amer. Chem. Soc., 62, 1154 (1940).

25 Alternatively, a compound of the formula VIII may also be prepared from a compound of the formula VII, wherein L¹ and L² are leaving groups such as methoxy, ethoxy, benzyloxy or chloro, preferably ethoxy, in the presence of a suitable catalyst, preferably rhodium(II)acetate according to the procedure described by M. Campbell et al., Aust. J. Chem., 45, 2061 (1992).

Compounds of the formula VI and VII are commercially available or easily obtained from readily available starting materials according to methods well known to those skilled in the art.
30 For example compounds of the Formula VII may be prepared according to the method of D. W. Peace et al., Synthesis, 658 (1971).

Compounds of the formula III (H_2NCONH_2) are commercially available or may be prepared by methods well known to those skilled in the art.

35 Scheme 3 refers to an alternate preparation of compounds of the formula I; in particular those wherein X is -O- or -OCH₂- . Referring to Scheme 3, a compound of the formula I, wherein X is -O-, may be obtained by reacting a compound of the formula XI with a suitable compound of the formula HO-A-Y-B-G according to the method of O. Mitsonubu

(*Synthesis*, 1 (1981)). A compound of the formula I, wherein X is $-OCH_2-$, may be obtained by reacting a compound of the formula XI with a suitable alkylating agent of the formula $L^3CH_2-A-Y-B-G$, wherein L^3 is a leaving group such as halo, p-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), preferably halo, most preferably chloro or bromo, in a suitable solvent 5 in the presence of a suitable base. Suitable solvents include acetonitrile, N,N-dimethylformamide or tetrahydrofuran. Suitable bases include sodium hydride, potassium carbonate, triethylamine, pyridine or triethanolamine. The aforesaid reaction may be conducted at a temperature of about 0°C to about 50°C, preferably about 20°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

10 Compounds of the formula XI may be prepared from a compound of the formula X according to the method of J. A. Vida *et al.*, *J. Med. Chem.*, 17, 732 (1974).

Compounds of the formula X may be prepared by reacting a compound of the formula XII with a suitable base, in the presence of a suitable alkylating agent and a solvent, such as described in Biehl *et al.*, *J. Het. Chem.*, 23, 9 (1986). Suitable bases include sodium hydride, 15 potassium carbonate, triethylamine, pyridine, or triethanolamine; preferably triethanolamine. Suitable alkylating agents include those of the formula R^1L^4 wherein L^4 is halo, p-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), preferably halo, most preferably chloro or bromo; or alkylating agents such as Eshenmoser's Salt, epoxides or suitably substituted electrophilic aziridines. Suitable solvents depend upon the base used but may be chosen from N,N-dimethylformamide, 20 tetrahydrofuran, acetonitrile or water. The aforesaid reaction may be conducted at a temperature of about 0°C to about 30°C, preferably about 20°C to about 25°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

Compounds of the formula XII are commercially available or may be easily prepared by those skilled in the art according to the methods reviewed in *The Organic Chemistry of Drug 25 Synthesis*, D. Lednicer and L. A. Mitscher, Volume 1, pages 167 to 277 and references cited therein.

Scheme 4 refers to yet an alternate preparation of compounds of the formula I. Referring to Scheme 4, a compound of the formula I may be obtained by reacting a compound of formula XIV with a compound of the formula H-X-A-Y-B-G in the presence of a base. 30 Suitable bases include polymer bound bases such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (PTBD) crosslinked with 2% divinyl benzene (DVB) or alkali metal carbonates, preferably PTBD. Suitable solvents include alcohols (such as ethanol, methanol and butanol), dimethylformamide, tetrahydrofuran or acetonitrile, preferably absolute acetonitrile. The aforesaid reaction may be conducted at a temperature of about 20°C to about 90°C, 35 preferably about 50°C to about 65°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

The compound of formula XIV is prepared by reacting a compound of formula X with a suitable bromination reagent such as Br₂ or Br₂-Ph₃P in an inert solvent. Suitable solvents include water (in the presence of a suitable base, such as aqueous sodium hydroxide), acetic acid, acetonitrile or dimethylformamide, preferably water. The aforesaid reaction may be 5 conducted at a temperature of about 0°C to about 40°C, preferably about 20°C to about 35°C. The aforesaid reaction may be conducted for a time period between about 15 minutes to about 16 hours.

Alternatively, compounds of the formula I, wherein X is -S- or -SCH₂-, or wherein X is >SO₂, >SO, -SO₂CH₂-, or -SOCH₂-, may be prepared by reacting a compound of the formula 10 X with a suitable disulfide of the formula (S-A-Y-B-G)₂ or (S-CH₂-A-Y-B-G)₂ in a suitable solvent in the presence of a suitable base. Suitable solvents include N,N-dimethylformamide, tetrahydrofuran, or acetonitrile. Suitable bases include sodium hydride, potassium carbonate, triethylamine, pyridine or triethanolamine. The aforesaid reaction may be conducted at a temperature of about 20°C to about 70°C, preferably about 20°C. The aforesaid reaction may be 15 conducted for a time period between about 15 minutes to about 16 hours.

Disulfides of the formula (S-A-Y-B-G)₂ or (S-CH₂-A-Y-B-G)₂ may be prepared from the corresponding thiols of the formula H-S-A-Y-B-G or H-S-CH₂-A-Y-B-G by oxidative methods well known to those skilled the art.

Compounds of the formula X are commercially available, or may be made by methods 20 of scheme 3, or may be made by methods well known to those skilled in the art.

One skilled in the art will also appreciate that the side chains denoted R¹ and -X-A-Y-B-G may be added as a unit, as is discussed above in schemes 1-4, or may be added as separate modules such as X-A followed by the addition of a second unit L'-Y-B-G, wherein L' is a suitable leaving group. Such methods are well known to those skilled in the art.

25 Scheme 5 describes the preparation of the side chain unit of the formula and -X-A-Y-B-G, which is used to prepare compounds of formula I in Schemes 1-4. Referring to Scheme 5, a compound of the formula XV, wherein X' is >(C=O)-Cl may be prepared by reacting a compound of the formula XVI, wherein -X-P is >(C=O)-OH, with a chlorinating agent. Suitable chlorinating agents include thionyl chloride or phosphorous oxychloride. A compound of the 30 formula XV, wherein X' is -OH, -SH, >NHR⁵, -CH₂OH, -CH₂SH, -CH₂NHR⁵ or -SO₂NHR⁵, may be prepared by reacting an appropriate compound of formula XVI, wherein X-P is a protected form of -OH, -SH, >NHR⁵, -CH₂OH, -CH₂SH, -CH₂NHR⁵ or -SO₂NHR⁵, with a protecting group removal agent under conditions commonly known to those of ordinary skill in the art and referenced in Greene and Wuts, "Protecting Groups in Organic Synthesis," (John Wiley & Son Press, 2nd Ed).

Compounds of the formula XVI, wherein Y is -O-, -S-, -CH₂O-, -CH₂S-, >NR⁶, -CH₂NR⁶ or SO₂NR⁶, may be prepared by reacting a compound of formula XVII, wherein M is

Br or I, with a compound of the formula G-B-Y-H in the presence of a suitable base in the presence of a suitable catalyst in a polar aprotic solvent. Suitable bases include alkali metal carbonate or hydroxide base, preferably potassium carbonate. Suitable catalysts include a copper (0) catalyst, preferably finely powdered copper bronze. Suitable solvents include 5 dimethylformamide or 1-methyl-2-pyrrolidinone. The aforesaid reaction may be conducted at a temperature between about 80°C and 140°C. The aforesaid reaction may be conducted for about 6 to 24 hours.

Alternatively, compounds of the formula XVI, wherein Y is -O-, -S-, -CH₂O-, -CH₂S-, >NR⁶, -CH₂NR⁶ or SO₂NR⁶, may be prepared by reacting a compound of formula XVII, 10 wherein M is Cl, Br, I or triflate (TfO), with a compound of the formula G-B-Y-H under Buchwald and Hartwig's conditions in the presence of a suitable base, a palladium (0) catalyst and a suitable ligand in a suitable solvent. Suitable bases include an alkoxide base, preferably sodium *tert*-butoxide. Suitable catalysts include Pd₂(dba)₃. Suitable ligands include a triaryl phosphine ligand, preferably tri(*ortho*-tolyl)phosphine. Suitable solvents include an ethereal 15 solvent, preferably dioxane. The aforesaid reaction may be conducted at a temperature of about 40°C to about 100°C. The aforesaid reaction may be conducted for about 1 hour to 48 hours. Such conditions are reviewed in *Angew. Chem. Int. Ed. Engl.* 1998, 37, 2046-2067 and are well known to those of ordinary skill in the art.

Alternatively, compounds of the formula XVI, wherein Y is -O-, -S-, -CH₂O-, -CH₂S-, >NR⁶, -CH₂NR⁶ or SO₂NR⁶, may be prepared by reacting a compound of formula XVII, 20 wherein M is B(OH)₂, with a compound of the formula G-B-Y-H under an atmosphere of oxygen gas in the presence of a copper catalyst, 4 angstrom molecular sieves and a suitable tertiary amine base in a suitable solvent. Suitable catalysts include copper (II) acetate. Suitable bases include triethylamine or pyridine. Suitable solvents include methylene chloride, 25 dimethyl sulfoxide, or tetrahydrofuran. The aforesaid reaction may be conducted at a temperature of about 10°C to about 50°C, preferably about 23°C. The aforesaid reaction may be conducted for about 6 hour to 72 hours.

Compounds of the formula XVI, wherein Y is -CH₂O-, -CH₂S-, -CH₂[N(R⁶)]- or -SO₂[N(R⁶)]-, and wherein -X-P is -OH, may be prepared by a three step 30 reaction from a compound of the formula XVI, wherein X-P is -COR, wherein R is alkyl or aryl. First, compounds of the formula XVI, wherein -X-P is -OH, may be prepared by reacting a compound of formula XVI, wherein X-P is -OCOR, wherein R is alkyl or aryl, with a suitable base, such as a hydroxide base, preferably lithium hydroxide, in a mixture of methanol and water by ester hydrolysis conditions known by those skilled in the art. Second, the compound 35 of formula XVI, wherein X-P is -OCOR, wherein R is alkyl or aryl, may be prepared by reacting a compound of formula XVI, wherein X-P is -COR, wherein R is alkyl or aryl, by so-called Baeyer Villager oxidation conditions, which is a classical organic transformation and well

known to those of ordinary skill in the art. Third, the compound of formula XVI, wherein X-P is -COR, wherein R is alkyl or aryl, may be prepared by reacting a compound of formula XVII, wherein X-P is -COR and M is F, with a compound of the formula W-G-B-Y-H in the presence of a suitable base in a polar aprotic solvent. Suitable bases include an alkali metal hydride 5 base, preferably sodium hydride. Suitable solvents include dimethylformamide or tetrahydrofuran. The aforesaid reaction may be conducted at a temperature of about 0°C to about 140°C. The aforesaid reaction may be conducted for about 1 hour to about 24 hours.

Compounds of the formula XVI, wherein Y is -CH₂O-, -CH₂S-, -CH₂[N(R⁶)]- or -SO₂[N(R⁶)]-, and wherein X-P is >NR⁵, may be prepared by a two step 10 reaction from a compound of formula XVII, wherein X-P is -COR, wherein R is alkyl or aryl. First, a compound of the formula XVI, wherein Y is -CH₂O-, -CH₂S-, -CH₂[N(R⁶)]- or -SO₂[N(R⁶)]-, and wherein X-P is >NR⁵, may be prepared by reacting a compound of formula XVI, wherein X-P is -COR, wherein R is alkyl or aryl, by the so-called 15 Curtius rearrangement. The Curtius rearrangement is a classical organic transformation and well known to those of ordinary skill in the art. Second, the compound of formula XVI, wherein X-P is -COR, wherein R is alkyl or aryl, may be prepared by reacting a compound of formula XVII, wherein X-P is -COR, and M is F, with a compound of the formula W-G-B-Y-H in the presence of a suitable base in a polar aprotic solvent. Suitable bases include an alkali metal 20 hydride base, preferably sodium hydride. Suitable solvents include dimethylformamide or tetrahydrofuran. The aforesaid reaction may be conducted at a temperature of about 0°C to about 140°C. The aforesaid reaction may be conducted for about 1 hour to about 24 hours.

Compounds of the formula XVI, wherein Y is >SO₂, >S=O, -CH₂SO-, -CH₂SO₂-, -SOCH₂-, or -SO₂CH₂-, may be prepared by reacting the corresponding lower oxidation state 25 compounds of the formula XVI (e.g. wherein Y is -S-, -CH₂S-, or -SCH₂-) with a suitable oxidant in a suitable solvent. Suitable oxidants include a peroxy acid, preferably peracetic acid, or an organic peroxide, preferably *m*-chloroperoxybenzoic acid or *tert*-butyl hydroperoxide. Suitable solvents include methylene chloride or *tert*-butanol. The aforesaid reaction may be conducted at a temperature between about -10°C and about 30°C. The aforesaid reaction may be conducted for about 1 hour to about 8 hours.

Compounds of the formula XVI, wherein Y is -OCH₂-, -SCH₂-, or [N(R⁶)]CH₂- may be 30 prepared by reacting a compound of the formula XVII, wherein M is L-CH₂-, wherein L is halo, mesyloxy (MsO) or tosyloxy (TsO), with an appropriate compound of the formula G-B-Y-H, wherein Y is -O-, -S- or >NR⁶, in the presence of a suitable base, in the presence of a polar aprotic solvent. Suitable bases include an alkali metal carbonate base, preferably potassium 35 carbonate, or cesium carbonate. Suitable solvents include dimethylformamide or tetrahydrofuran. The aforesaid reaction may be conducted at a temperature between about 23°C and about 80°C, preferably about 20°C to about 50°C. The aforesaid reaction may be conducted for about 1 hour to about 24 hours.

Compounds of the formula XVI, wherein Y is $>\text{C}=\text{O}$ or $-\text{CH}=\text{CH}-$, may be prepared by reacting a compound of formula XVII, wherein M is $-\text{B}(\text{OH})_2$, $-\text{ZnBr}$, $-\text{ZnCl}$, or trialkyltin, with a compound of the formula G-B-Y-Z, wherein Z is halo, preferably Cl, Br or I, in the presence of a catalyst in a suitable solvent. Suitable catalysts include a palladium or nickel catalyst, preferably $\text{Pd}(\text{PPh}_3)_4$. Suitable solvents include toluene, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide. The aforesaid reaction may be conducted at a temperature between about 23 °C and about 110°C. The aforesaid reaction may be conducted for a period of about 1 hour to about 24 hours. The aforesaid reaction may be facilitated by the presence of a copper salt, such as cuprous iodide or cuprous bromide.

Compounds of the formula XVI, wherein Y is $-\text{C}\equiv\text{C}-$ may be prepared by reacting a compound of formula XVII, wherein M is halo or triflate, preferably Br or I, with a compound of the formula G-B-Y-H, in the presence of a suitable base and a catalyst in a suitable solvent. Suitable bases include a trialkylamine base, preferably triethylamine. Suitable catalysts include a palladium catalyst, preferably $\text{Pd}(\text{PPh}_3)_4$. Suitable solvents include tetrahydrofuran or dimethylformamide. The aforesaid reaction may be conducted at a temperature between about 23°C and about 60°C. The aforesaid reaction may be conducted for a period of about 1 hour to about 24 hours.

One of ordinary skill in the art will recognize that compounds of the formula XVI, wherein Y is $-\text{CH}_2\text{CH}_2-$, may be prepared by reacting the aforementioned compounds of the formula XVI, wherein Y is $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$, with a reducing agent in the presence of a palladium catalyst in a suitable solvent. Suitable reducing agents include hydrogen gas at ambient pressure to 50 psi. Preferred catalyst is palladium on charcoal. Suitable solvents include methanol or ethyl acetate. The aforesaid reaction may be conducted at a temperature between about 20°C and about 50°C. The aforesaid reaction may be conducted for about 1 hour to about 24 hours.

Compounds of the formula XVII, wherein P is a suitable protecting group as defined in Greene and Wuts, supra, are either commercially available, known, or may be prepared from commercially available starting materials by methods known to those of ordinary skill in the art.

Scheme 6 describes the preparation of compounds of the formula XVIII, wherein X is $-\text{OCH}_2-$, SCH_2- or $-\text{[N}(\text{R}^5)\text{]} \text{CH}_2-$. Compounds of the formula XVIII are compounds of formula IV in Scheme 1, wherein R^1 is hydrogen. Referring to Scheme 6, compounds of formula XVIII, wherein L^1 and L^2 are leaving groups such as methoxy, ethoxy, benzyloxy or chloro, preferably ethoxy, may be prepared by reacting a compound of formula XIX, wherein L^1 and L^2 are leaving groups as defined above, with a compound of formula G-B-Y-A-X-H, wherein X is $-\text{O}-$, $-\text{S}-$ or $>\text{NR}^5$, in the presence of a suitable base and a suitable solvent. Suitable bases include an alkali metal hydride base, preferably sodium hydride. Suitable solvents include an alcoholic

solvent, tetrahydrofuran, or dimethylformamide. The aforesaid reaction may be conducted at a temperature of about -20°C to about 50°C, preferably about 0°C to about 23°C. The aforesaid reaction may be conducted for about 1 hour to about 24 hours.

Scheme 7 describes an alternate preparation of compounds of formula I. Referring to Scheme 7, compounds of formula I may also be prepared by reacting a compound of formula XX, wherein X" is an unprotected X such as alcohol or phenol, with an appropriate compound of the formula XIV, which may be prepared according to the procedure of Scheme 4, in the presence of a suitable base in a polar aprotic solvent. Suitable bases include an alkali metal carbonate, such as cesium carbonate, preferably an alkali metal carbonate base, polymer bound amidine, or quanidine base, more preferably 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene. Suitable polar aprotic solvents include acetonitrile or dimethylformamide, preferably acetonitrile. The aforesaid reaction may be conducted at a temperature between about 0 °C and about 50 °C, preferably about 23 °C. The aforesaid reaction may be conducted for a period of 2 hours to 4 days.

Compounds of formula XX may be prepared by reacting a compound of formula XXI, wherein X-P is a protected X such as alkylated alcohol or alkylated phenol, with a suitable protecting group removal agent. Conditions for this deprotection reaction are well known to those skilled in the art and may be found in Greene and Wuts, "Protecting Groups in Organic Synthesis," (John Wiley & Sons, 2nd Ed). Preferred protecting groups include methyl. Suitable protecting group removal agents include sulfur containing amino acid, such as methionine, preferably dl methionine, or a quaternary ammonium halide salt, such as a quaternary ammonium iodide salt, preferably tetrabutylammonium iodide. When the protecting group removal agent used is sulfur containing amino acid, compounds of formula XX may be prepared by reacting a compound of formula XXI in an acidic solvent. Suitable solvents include a sulfonic acid solvent, preferably methanesulfonic acid solvent. The aforesaid reaction may be conducted at a temperature between about 0 °C and about 100 °C, preferably at about 23 to about 50 °C. The aforesaid reaction may be conducted for a period of 4 hours to 48 hours. When the protecting group removal agent used is a quaternary ammonium halide salt, compounds of formula XX may be prepared by reacting a compound of formula XXI in the presence of a suitable Lewis acid in a polar aprotic solvent. Suitable Lewis acids include a boron halide Lewis acid, preferably boron trichloride. Suitable solvents include a chlorinated hydrocarbon solvent, preferably methylene chloride. The aforesaid reaction may be conducted at a temperature between about -78 °C and about 50 °C, preferably about -78 °C to about 23 °C. The aforesaid reaction may be conducted for about 1 hour to about 24 hours.

Compounds of formula XXI, wherein G is alkyl, may be prepared by reacting a compound of formula XXII by with an appropriate alkylating agent in the presence of a suitable

base in a polar aprotic solvent. Suitable alkylating agents include an alkyl halide or alkyl sulfonate ester, preferably an alkyl iodide. Suitable bases include an alkali metal hydride, preferably sodium hydride, or an alkali metal carbonate, preferably potassium carbonate. Suitable polar aprotic solvents include dimethylformamide, *N,N*-dimethylacetamide, or 1-methyl-2-pyrrolidinone, preferably dimethylformamide. The aforesaid reaction may be conducted at a temperature between about 0 °C and about 100 °C, preferably about between 0 °C and about 50 °C. The aforesaid reaction may be conducted for a period of 1 hour to 24 hours.

Compounds of formula XXI, wherein G is aryl or heteroaryl, may be prepared by reacting a compound of formula XXII with an appropriate arylating agent or heteroaryloylating agent, in the presence of a suitable base and a polar aprotic solvent, and optionally in the presence of a catalyst. Suitable arylating agents include an aryl halide, preferably an aryl fluoride, bromide or iodide. Suitable heteroaryloylating agents include heteroaryl fluoride, bromide or iodide. Suitable bases include an alkali metal hydride, preferably sodium hydride, or an alkali metal carbonate, preferably potassium carbonate. Suitable polar aprotic solvents include dimethylformamide, *N,N*-dimethyl acetamide or 1-methyl-2-pyrrolidinone, preferably *N,N* dimethyl acetamide. Suitable catalysts include a copper (I) or copper (0) catalyst, preferably Cu₂O or copper bronze. The aforesaid reaction may be conducted at a temperature between about 0 °C and about 180 °C, preferably about 160 °C. The aforesaid reaction may be conducted for a period of 1 hour to 24 hours.

Alternatively, compounds of formula XXI, wherein G is aryl or heteroaryl, may be prepared by reacting a compound of formula XXII with an arylating agent or heteroaryloylating agent, such as an aryl boronic acid or heteroaryl boronic acid, in the presence of a suitable base, a polar aprotic solvent, a catalyst, and a water scavenger under an atmosphere of air or dry oxygen. Suitable bases include a tertiary amine base, preferably triethylamine or pyridine. Suitable polar aprotic solvents include methylene chloride or dimethyl sulfoxide. Suitable catalysts include copper (II) catalyst, such as Cu(OAc)₂. Suitable water scavengers include 4A molecular sieves. The aforesaid reaction may be conducted at a temperature of about 0 °C to about 50 °C. The aforesaid reaction may be conducted for a period of 1 hour to 21 days.

Compounds of formula XXII are generally well known to those of ordinary skill in the art. Alternatively, compounds of formula XXII may be prepared by reacting a compound of formula XIX, wherein P₂ is a protecting group, such as acetyl, under conditions described in Greene and Wuts, "Protecting Groups in Organic Synthesis," (John Wiley & Sons, 2nd Ed).

Compounds of formula XXIII may be prepared by reacting a compound of formula XXIV, wherein P₂ is a protecting group, such as acetyl, with a compound of formula XXV, wherein P is a protecting group, such as methyl or benzyl, in the presence of a copper (II) catalyst, a suitable base, a water scavenger a polar aprotic solvent under an atmosphere of air or dry oxygen. Suitable catalysts include Cu(OAc)₂. Suitable bases include a tertiary amine

base, preferably triethylamine or pyridine. Suitable water scavengers include 4A molecular sieves. Suitable solvents include methylene chloride or dimethyl sulfoxide. The aforesaid reaction may be conducted at a temperature of about 0 °C to about 50 °C. The aforesaid reaction may be conducted for a period of 1 hour to 21 days.

5 The compounds of the formula I, which are basic in nature, are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base
10 compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful
15 evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate,
20 lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts
25 include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such
30 pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure.

Alternatively, they may also be prepared by mixing lower alkanolic solutions of the
35 acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

BIOLOGICAL ASSAYS

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reproxins and, consequently, demonstrate their effectiveness for treating diseases characterized by metalloproteinase activity may be shown by the following *in vitro* and *in vivo* assay tests.

MMP Assays

MMP-13 selective inhibitors may be identified by screening the inhibitors of the present invention through the MMP fluorescence assays described below and selecting those agents with MMP-X/MMP-13 inhibition IC₅₀ ratios of 100 or greater and potency of less than 100 nM, where MMP-X refers to one or more other MMPs.

Non-selective collagenase inhibitors as used herein, unless otherwise mentioned, refer to agents which exhibit less than a 100 fold selectivity for the inhibition of MMP-13 enzyme activity over MMP-X enzyme activity or a potency of more than 100nM as defined by the IC₅₀ results from the MMP-13 and MMP-X fluorescence assays described below.

The ability of collagenase inhibitors to inhibit collagenase activity is well known in the art. The degree of inhibition of a particular MMP for several compounds has been well documented in the art and those skilled in the art will know how to normalize different assay results to those assays reported herein. The following assays may be used to identify matrix metalloproteinase inhibitors.

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin. The amount of trypsin may be optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 µg trypsin per 100 µg of collagenase. The trypsin and collagenase may be incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

Stock solutions (10 mM) of inhibitors may be made up in dimethylsulfoxide and then diluted using the following scheme:

10 mM -----> 120 µM -----> 12 µM -----> 1.2 µM -----> 0.12 µM

Twenty-five microliters of each concentration may then be added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor may be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) may be set up in wells D7-D12 and negative controls (no enzyme, no inhibitors) may be set in wells D1-D6.

Collagenase-1 may be diluted to 240 ng/ml and 25 µl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay may be 60 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) may be made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 µM in assay buffer. The assay may be

initiated by the addition of 50 µl substrate per well of the microfluor plate to give a final concentration of 10 µM.

Fluorescence readings (360 nM excitation, 460 nm emission) may be taken at time 0 and then at 20 minute intervals. The assay may be conducted at room temperature with a typical
5 assay time of 3 hours.

Fluorescence versus time may be then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least five fold over the blank) and that is on a linear part of the curve (usually around 120 minutes) may be chosen to determine IC₅₀ values. The zero time may be used as a
10 blank for each compound at each concentration and these values may be subtracted from the 120-minute data. Data may be plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC₅₀'s may be determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC₅₀'s are reported to be less than 0.03 µM then the inhibitors may be assayed at
15 concentrations of 0.3 µM, 0.03 µM and 0.003 µM.

Inhibition of Gelatinase (MMP-2)

Human recombinant 72 kD gelatinase (MMP-2, gelatinase A) may be activated for 16-18 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 4°C, rocking gently.

20 10 mM dimethylsulfoxide stock solutions of inhibitors may be diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 µM ZnCl₂ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM---> 120 µM---> 12 µM---> 1.2 µM---> 0.12 µM

Further dilutions may be made as necessary following this same scheme. A minimum of four
25 inhibitor concentrations for each compound may be performed in each assay. 25 µL of each concentration may be then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume may be 100 µL, final concentrations of inhibitor may be the result of a further 1:4 dilution (i.e. 30 µM ---> 3 µM ---> 0.3 µM ---> 0.03 µM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) may be
30 also prepared in triplicate.

Activated enzyme may be diluted to 100 ng/mL in assay buffer, 25 µL per well may be added to appropriate wells of the microplate. Final enzyme concentration in the assay may be 25 ng/mL (0.34 nM).

A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) may be diluted in assay buffer to 20 µM. The assay may be initiated by addition of 50 µL of diluted substrate yielding a final assay concentration of 10 µM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) may be immediately taken and

subsequent readings may be taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank may be plotted versus time. An early time point on the linear part of this curve may be chosen for IC₅₀ determinations. The zero time point for each compound at each dilution may be subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data may be plotted as inhibitor concentration versus percent of enzyme control. IC₅₀'s may be defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

10

Inhibition of Stromelysin Activity (MMP-3)

Human recombinant stromelysin (MMP-3, stromelysin-1) may be activated for 20-22 hours with 2 mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

15

10 mM dimethylsulfoxide stock solutions of inhibitors may be diluted serially in assay buffer (50 mM TRIS, pH 7.5, 150 mM NaCl, 10 mM CaCl₂ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM → 120 μM → 12 μM → 1.2 μM → 0.12 μM

20

Further dilutions may be made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound may be performed in each assay. 25 μL of each concentration may be then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume may be 100 μL, final concentrations of inhibitor may be the result of a further 1:4 dilution (i.e. 30 μM → 3 μM → 0.3 μM → 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) may be also prepared in triplicate.

25

Activated enzyme is diluted to 200 ng/mL in assay buffer, 25 μL per well may be added to appropriate wells of the microplate. Final enzyme concentration in the assay may be 50 ng/mL (0.875 nM).

30

A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH₂) may be diluted in assay buffer to 6 μM. The assay may be initiated by addition of 50 μL of diluted substrate yielding a final assay concentration of 3 μM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) may be immediately taken and subsequent readings may be taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

35

The average value of fluorescence of the enzyme and blank may be plotted versus time. An early time point on the linear part of this curve may be chosen for IC₅₀ determinations. The zero time point for each compound at each dilution may be subtracted

from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data may be plotted as inhibitor concentration versus percent of enzyme control. IC₅₀'s may be defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

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Inhibition of Human 92 kD Gelatinase (MMP-9)

Inhibition of 92 kD gelatinase (MMP-9) activity may be assayed using the Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂ substrate (10 μM) under similar conditions as described above for the inhibition of human collagenase (MMP-1).

Human recombinant 92 kD gelatinase (MMP-9, gelatinase B) may be activated for 2 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37 C.

10 10 mM dimethylsulfoxide stock solutions of inhibitors may be diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μM ZnCl₂, 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

15 10 mM----> 120 μM----> 12 μM----> 1.2 μM----> 0.12 μM

Further dilutions may be made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound may be performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume may be 100 μL, final concentrations of inhibitor may be the result of a further 1:4 dilution (i.e. 30 μM ----> 3 μM ----> 0.3 μM ----> 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) may be also prepared in triplicate.

20 Activated enzyme may be diluted to 100 ng/mL in assay buffer, 25 μL per well may be added to appropriate wells of the microplate. Final enzyme concentration in the assay may be 25 ng/mL (0.27 nM).

25 A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) may be diluted in assay buffer to 20 μM. The assay may be initiated by addition of 50 μL of diluted substrate yielding a final assay concentration of 10 μM substrate. A zero time fluorescence reading (320 excitation; 390 emission) may be immediately taken and subsequent readings may be taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

30 The average value of fluorescence of the enzyme and blank may be plotted versus time. An early time point on the linear part of this curve may be chosen for IC₅₀ determinations. The zero time point for each compound at each dilution may be subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data may be plotted

as inhibitor concentration versus percent of enzyme control. IC₅₀'s may be defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of MMP-13

5 Human recombinant MMP-13 may be activated with 2 mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and may be diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5 mM calcium chloride, 20 µM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme may be added per well of a 96 well microfluor plate. The enzyme may be then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 10 mM stock solutions of inhibitors may be made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration may be added in triplicate to the microfluor plate. The final concentrations in the assay may be 30 µM, 3 µM, 0.3 µM and 0.03 µM.

15 Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) may be prepared as for inhibition of human collagenase (MMP-1) and 50 µl may be added to each well to give a final assay concentration of 10 µM. Fluorescence readings (360 nM excitation; 450 emission) may be taken at time 0 and every 5 minutes for 1 hour.

Positive controls may consist of enzyme and substrate with no inhibitor and blanks 20 consist of substrate only.

IC₅₀'s may be determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 µM, inhibitors may be then assayed at final concentrations of 0.3 µM, 0.03 µM, 0.003 µM and 0.0003 µM.

Collagen film MMP-13 Assay

25 Rat type I collagen may be radiolabeled with ¹⁴C acetic anhydride (T.E. Cawston and A.J. Barrett, Anal. Biochem., 99, 340-345 (1979)) and used to prepare 96 well plates containing radiolabeled collagen films (Barbara Johnson-Wint, Anal. Biochem., 104, 175-181 (1980)). When a solution containing collagenase were added to the well, the enzyme cleaves the insoluble collagen which unwinds and would thus solubilized. Collagenase activity may be 30 directly proportional to the amount of collagen solubilized, determined by the proportion of radioactivity released into the supernatant as measured in a standard scintillation counter. Collagenase inhibitors may be, therefore, compounds which reduce the radioactive counts released with respect to the controls with no inhibitor present. One specific embodiment of this assay may be described in detail below.

35 For determining the selectivity of compounds for MMP-13 versus MMP-1 using collagen as a substrate, the following procedure may be used. Recombinant human proMMP-13 or proMMP-1 may be activated according to the procedures outlined above. The activated

MMP-13 or MMP-1 may be diluted to 0.6 µg/ml with buffer (50 mM Tris pH 7.5, 150 mM NaCl, 10 mM CaCl₂, 1 µM ZnCl₂, 0.05% Brij-35, 0.02% sodium azide).

Stock solutions of test compound (10mM) in dimethylsulfoxide may be prepared. Dilutions of the test compounds in the Tris buffer, above, may be made to 0.2, 2.0, 20, 200, 5 2000 and 20000 nM.

100 µl of appropriate drug dilution and 100 µl of diluted enzyme may be pipetted into wells of a 96 well plate containing collagen films labeled with ¹⁴C-collagen. The final enzyme concentration may be 0.3 µg/ml while the final drug concentration is 0.1, 1.0, 10, 100, 1000 nM. Each drug concentration and control may be analyzed in triplicate. Triplicate controls 10 may be also run for the conditions in which no enzyme may be present and for enzyme in the absence of any compound.

The plates may be incubated at 37°C for a time period such that around 30 - 50% of 15 the available collagen may be solubilized. The time period may be determined by counting additional control wells at various time points. In most cases around 9 hours of incubation may be required. When the assay has progressed sufficiently, the supernatant from each well 20 may be removed and counted in a scintillation counter. The background counts (determined by the counts in the wells with no enzyme) may be subtracted from each sample and the % release calculated in relation to the wells with enzyme only and no inhibitor. The triplicate values for each point may be averaged and the data graphed as percent release versus drug concentration. IC₅₀'s may be determined from the point at which 50% inhibition of release of radiolabeled collagen may be obtained.

To determine the identity of the active collagenases in cartilage conditioned medium, assays may be conducted using collagen as a substrate, cartilage conditioned medium containing collagenase activity and inhibitors of varying selectivity. The cartilage conditioned 25 medium may be collected during the time at which collagen degradation may be occurring and thus may be representative of the collagenases responsible for the collagen breakdown. Assays may be conducted as outlined above except that instead of using recombinant MMP-13 or recombinant MMP-1, cartilage conditioned medium may be the enzyme source.

IL-1 Induced Cartilage Collagen Degradation From Bovine Nasal Cartilage

30 This assay may use bovine nasal cartilage explants which are commonly used to test the efficacy of various compounds to inhibit either IL-1 induced proteoglycan degradation or IL-1 induced collagen degradation. Bovine nasal cartilage is a tissue that is very similar to articular cartilage, i.e. chondrocytes surrounded by a matrix that is primarily type II collagen and aggrecan. The tissue may be used because it: (1) is very similar to articular cartilage, (2) 35 is readily available, (3) is relatively homogeneous and (4) degrades with predictable kinetics after IL-1 stimulation.

Two variations of this assay may be used to assay compounds. Both variations may give similar data. The two variations may be described below:

Variation 1

Three plugs of bovine nasal cartilage (approximately 2 mm diameter x 1.5 mm long) 5 may be placed into each well of a 24 well tissue culture plate. One ml of serumless medium may be then added to each well. Compounds may be prepared as 10 mM stock solutions in dimethyl sulfoxide and then diluted appropriately in serumless medium to final concentrations, e.g., 50, 500 and 5000 nM. Each concentration may be assayed in triplicate.

Human recombinant IL-1 α (5ng/mL) (IL-1) may be added to triplicate control wells and 10 to each well containing drug. Triplicate control wells may be also set up in which neither drug nor IL-1 may be added. The medium may be removed and fresh medium containing IL-1 and the appropriate drug concentrations may be added on days 6, 12, 18 and 24 or every 15 3 - 4 days if necessary. The media removed at each time point may be stored at -20°C for later analysis. When the cartilage in the IL-1 alone wells may have been almost completely resorbed (about day 21), the experiment may be terminated. The medium may be removed and stored. Aliquots (100 μ l) from each well at each time point may be pooled, digested with papain and then analyzed for hydroxyproline content. Background hydroxyproline (average of wells with no IL-1 and no drug) may be subtracted from each data point and the average calculated for each triplicate. The data may be then expressed as a percent of the IL-1 alone 20 average value and plotted. The IC₅₀ may be determined from this plot.

Variation 2

The experimental set-up may be the same as outlined above in Variation 1, until day 12. On day 12, the conditioned medium from each well may be removed and frozen. Then 25 one ml of phosphate buffered saline (PBS) containing 0.5 μ g/ml trypsin may be added to each well and incubation continued for a further 48 hours at 37°C. After 48 hours incubation in trypsin, the PBS solution may be removed. Aliquots (50 μ l) of the PBS/trypsin solution and the previous two time points (days 6 and 12) may be pooled, hydrolyzed and hydroxyproline content determined. Background hydroxyproline (average of wells with no IL-1 and no drug) 30 may be subtracted from each data point and the average calculated for each triplicate. The data may be then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ may be determined from this plot. In this variation, the time course of the experiment v 35 shortened considerably. The addition of trypsin for 48 hours after 12 days of IL-1 stimulation likely releases any type II collagen that may have been damaged by collagenase activity but not yet released from the cartilage matrix. In the absence of IL-1 stimulation, trypsin treatment may produce only low background levels of collagen degradation in the cartilage explants.

Inhibition of TNF Production

The ability or inability of the compounds or the pharmaceutically acceptable salts thereof

to inhibit the production of TNF may be shown by the following in vitro assay:

Human Monocyte Assay

Human mononuclear cells may be isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. The mononuclear cells may be washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2×10^6 /ml in HBSS containing 1% BSA. Differential counts may be determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180 μ l of the cell suspension may be aliquoted into flat bottom 96 well plates (Costar).
10 Additions of compounds and LPS (100 ng/ml final concentration) may give a final volume of 200 μ l. All conditions may be performed in triplicate. After a four hour incubation at 37°C in an humidified CO₂ incubator, plates may be removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF α using the R&D ELISA Kit.

Aggrecanase Assay

15 Primary porcine chondrocytes from articular joint cartilage may be isolated by sequential trypsin and collagenase digestion followed by collagenase digestion overnight and may be plated at 2×10^5 cells per well into 48 well plates with 5 μ Ci / ml ³⁵S (1000 Ci/mmol) sulfur in type I collagen coated plates. Cells may be allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C, under an atmosphere of 5% CO₂.

20 The night before initiating the assay, chondrocyte monolayers may be washed two times in DMEM/ 1% PSF/G and then allowed to incubate in fresh DMEM /1% FBS overnight.

The following morning chondrocytes may be washed once in DMEM/1%PSF/G. The final wash may be allowed to sit on the plates in the incubator while making dilutions.

Media and dilutions may be made as described in the Table below.

Control Media	DMEM alone (control media)
IL-1 Media	DMEM + IL-1 (5 ng/ml)
Drug Dilutions	<p>Make all compounds stocks at 10 mM in DMSO.</p> <p>Make a 100 μM stock of each compound in DMEM in 96 well plate. Store in freezer overnight.</p> <p>The next day perform serial dilutions in DMEM with IL-1 to 5 μM, 500 nM and 50 nM.</p> <p>Aspirate final wash from wells and add 50 μl of compound from above dilutions to 450 μl of IL-1 media in appropriate wells of the 48 well plates.</p> <p>Final compound concentrations equal 500 nM, 50 nM and 5 nM.</p> <p>All samples completed in triplicate with Control and IL-1 alone samples on each plate.</p>

Plates may be labeled and only the interior 24 wells of the plate may be used. On one of the plates, several columns may be designated as IL-1 (no drug) and Control (no IL-1, no drug). These control columns may be periodically counted to monitor 35S-proteoglycan release. Control and IL-1 media may be added to wells (450 μ l) followed by compound (50 μ l) so as to initiate the assay. Plates may be incubated at 37°C, with a 5% CO₂ atmosphere.

At 40-50 % release (when CPM from IL-1 media were 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay may be terminated (9-12 hours). Media may be removed from all wells and placed in scintillation tubes. Scintillate may be added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 μ l of papain digestion buffer (0.2 M Tris, pH 7.0, 5 mM EDTA, 5 mM DTT and 1 mg/ml papain) may be added to each well. Plates with digestion solution may be incubated at 60°C overnight. The cell layer may be removed from the plates the next day and placed in scintillation tubes. Scintillate may be then added and samples counted (LSC).

The percent of released counts from the total present in each well may be determined. Averages of the triplicates may be made with control background subtracted from each well. The percent of compound inhibition may be based on IL-1 samples as 0% inhibition (100% of total counts).

The compounds of the present invention that were tested all have IC₅₀'s in at least one of the above assays of less than 100 μ M preferably less than 100nM. Certain preferred groups of compounds possess differential selectivity toward the various MMPs or ADAMs. One group of preferred compounds possesses selective activity towards MMP-13 over MMP-1. Another preferred group of compounds possesses selective activity towards MMP-13 over

MMP-1, MMP-3 and MMP-7. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-3, MMP-7 and MMP-17. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-14. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-12 and MMP-14.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases, a variety of conventional routes may be used including oral, parenteral (e.g., intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the compounds of the invention (hereinafter also known as the active compounds) will be administered at dosages of about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage may necessarily occur depending on the condition of the subject being treated. The person responsible for administration may, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention may be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention may present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc may often very useful for tabletting purposes.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they may be advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient may usually be prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions may be suitable intravenous injection purposes.

The oily solutions may be suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions may be readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds may be administered intramuscularly or subcutaneously at 5 dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

10 For intranasal administration or administration by inhalation, the active compounds of the invention may be conveniently delivered in the form of a solution or suspension from a pump spray container that may be squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon 15 dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder 20 base such as lactose or starch.

For topical ocular administration, direct application to the affected eye may be employed in the form of a formulation as eyedrops, aerosol, gels or ointments, or may be incorporated into collagen (such as poly-2-hydroxyethylmethacrylate and co-polymers thereof), or a hydrophilic polymer shield. The materials may also be applied as a contact lens or via a local reservoir or as 25 a subconjunctival formulation.

For intraorbital administration a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in an aqueous solution or suspension (particle size less than 10 micron) may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH between 5 and 8, if 30 necessary and the liquid diluent first rendered isotonic. Small amounts of polymers may be added to increase viscosity or for sustained release (such as cellulosic polymers, Dextran, polyethylene glycol, or alginic acid). These solutions may be suitable for intraorbital injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of 35 animals, compounds may be administered intraorbitally at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

As with the other routes of administration and corresponding dosage forms described herein, dosage forms intended for oral administration may be also suitably formulated to

provide controlled-, sustained- and/or delayed release of the active ingredient. Typically, these would include delayed-release oral tablets, capsules and multiparticulates, as well as enteric-coated tablets and capsules which prevent release and adsorption of the active ingredient in the stomach of the patient and facilitate enteric delivery distal to the stomach, i.e., 5 in the intestine. Other typical oral dosage forms may include sustained-release oral tablets, capsules and multiparticulates which provide systemic delivery of the active ingredient in a controlled manner over a prolonged period of time, e.g., a 24-hour period. Where rapid delivery of the active ingredient is required or desirable, a controlled-release oral dosage form 10 may be prepared in the form of a fast-dissolving tablet, which would also preferably include highly soluble salt forms of the active ingredient.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points were uncorrected. NMR data were reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. 15 Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure or *in vacuo* means that a rotary evaporator was used.

20

Example 1

5-[4-[2-(2-Ethoxy-ethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yloxy]-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
1		497	498.5

A mixture of 23 milligrams of 2-(2-Ethoxy-ethyl)-5-(4-hydroxy-phenoxy)-2,3-dihydro-25 isoindol-1-one (0.07 mmol), 5-bromo-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione (0.021 grams, 0.08 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (0.087 grams) and acetonitrile (0.5 mL) was shaken for 18 hours at room temperature. The mixture was treated with a solution of acetic acid in methanol (1:4 v/v), shaken for 20 minutes, and was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel

chromatography using 5% methanol in methylene chloride as eluant. Trituration of the purified product with *iso*-propyl ether afforded 5-{4-[2-(2-Ethoxy-ethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione (0.023 grams) as a colorless solid. MS: 498.5 [M+H]⁺; 496.5 [M-H]⁻

5 Preparation 1: 4-Bromo-2-methylbenzoic acid methyl ester:

A mixture of 4-bromo-2-methylbenzoic acid (20 grams, 215 mmol), methanol (500 mL) and concentrated sulfuric acid (1 mL) was refluxed for 8 hours. The mixture was concentrated *in vacuo*, diluted with ether, washed twice with water, and the organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*, affording 17 grams of 4-bromo-2-methylbenzoic acid methyl ester. ¹H NMR (CDCl₃, 500 MHz): δ 7.77 (d, 1H, J = 8.3 Hz), 7.41 (s, 1H), 7.37 (d, 1H, J = 8.3 Hz), 3.89 (s, 3H), 2.58 (s, 3H) ppm.

10 Preparation 2: 4-(4-Methoxy-phenoxy)-2-methyl-benzoic acid methyl ester:

A mixture of 4-methoxyphenol (12 grams, 52.4 mmol), 4-bromo-2-methylbenzoic acid methyl ester (12 grams, 52 mmol), potassium carbonate (14.5 grams, 105 mmol) and copper powder (3.3 grams, 52 mmol) was stirred at 200 °C for 12 hours. The mixture was cooled to 25 °C, diluted with diethylether, and the organic phase was washed twice with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (5% ether in hexanes) afforded 4.0 grams of 4-(4-Methoxy-phenoxy)-2-methyl-benzoic acid methyl ester. MS: 273.2 [M+H]⁺

15 Preparation 3: 2-Bromomethyl-4-(4-methoxy-phenoxy)-benzoic acid methyl ester:

To a mixture of 4-(4-Methoxy-phenoxy)-2-methyl-benzoic acid methyl ester (2.8 grams, 10.3 mmol), *N*-bromosuccinimide (2.14 grams, 12 mmol) and carbon tetrachloride (12 mL) was added a crystal of benzoyl peroxide. The mixture was heated to reflux for 2 hours, and an additional 2.1 grams of *N*-bromosuccinimide was added. After refluxing for an additional 4 hours, the mixture was cooled to room temperature, diluted with ether, and the organic phase was washed with water, dried over magnesium sulfate, filtered and concentrated, affording 3 grams of 2-Bromomethyl-4-(4-methoxy-phenoxy)-benzoic acid methyl ester as a colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.96 (d, 1H, J = 8.8 Hz), 7.05-6.90 (m, 6H), 6.87 (dd, 1H, J = 2.6, 8.3 Hz), 4.92 (s, 2H), 3.93 (s, 3H), 3.85(s, 3H) ppm.

20 Preparation 4: 2-(2-Ethoxy-ethyl)-5-(4-hydroxy-phenoxy)-2,3-dihydro-isoindol-1-one:

To a mixture of 2-Bromomethyl-4-(4-methoxy-phenoxy)-benzoic acid methyl ester (0.2 grams, 0.57 mmol) and 3 mL of ethanol was added ethoxyethylamine (0.073 mL, 0.062 grams, 0.70 mmol) and triethylamine (0.098 mL, 0.071 grams, 0.7 mmol). After shaking for 4 hours at 50 °C, the mixture was cooled to room temperature and concentrated under a stream of nitrogen. The residue was treated with methanesulfonic acid (3 mL) and methionine (0.13 grams). The mixture was shaken for 24 hours at room temperature and was then heated to 50 °C for 6 hours. After cooling to room temperature, the mixture was poured into aqueous 5

M sodium hydroxide with cooling in an ice bath, and the pH was adjusted to 8 with aqueous sodium bicarbonate. The aqueous phase was extracted 3 times with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by radial chromatography (2 mm silica gel plate) eluting with 3% methanol-
5 methylene chloride afforded 30 miligrams of 2-(2-Ethoxy-ethyl)-5-(4-hydroxy-phenoxy)-2,3-dihydro-isoindol-1-one as a colorless syrup. MS: 314.3 [M+H]⁺

Example 2
5-(2-Methoxy-ethyl)-5-[4-(1-pyridin-3-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
2		487	488.2

10

A mixture of 4-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-phenol (0.10 grams, 0.33 mmol), 2-methoxyethylbromobarbiturate (0.12 grams, 0.4 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (0.44 grams) and acetonitrile (3 mL) was shaken for 48 hours at room temperature. The mixture was treated with a solution of acetic acid in methanol (1:4 v/v),
15 shaken for 20 minutes, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography eluting with an ethyl acetate-hexanes gradient (0-100% ethyl acetate). Trituration of the purified product with *iso*-propyl ether afforded the title compound (0.055 grams) as a colorless solid. MS: 488.2 [M+H]⁺; 486.2 [M-H]⁻

Preparation 1: 4-(4-Methoxy-phenoxy)-2-methylnitrobenzene

To a mixture of 5-fluoro-2-nitrotoluene (7.0 grams, 45 mmol), 4-methoxyphenol (6.2 grams, 50 mmol) and dimethylformamide (45 mL) was added potassium *tert*-butoxide (5.1 grams, 45 mmol). After stirring at room temperature for 24 hours, the mixture was diluted with water, acidified with 1M aqueous hydrochloric acid, and the aqueous phase was extracted 3 times with ether. The combined organic layers were dried over magnesium sulfate, filtered
25 and concentrated *in vacuo*. Purification by silica gel chromatography eluting with 0-20% ethyl acetate-hexane afforded 3.5 grams of 4-(4-methoxy-phenoxy)-2-methylnitrobenzene as a yellow solid.

Preparation 2: 4-(4-methoxy-phenoxy)-2-methyl-phenylamine

A mixture of 4-(4-methoxy-phenoxy)-2-methylnitrobenzene (3.5 grams, mmol) and
30 methanol (200 mL) was treated with 200 miligrams of 10% palladium on carbon and was

shaken under 50 psi of hydrogen gas for 3 hours. Filtration through a pad of celite and concentration *in vacuo* afforded 3.1 grams of 4-(4-methoxy-phenoxy)-2-methyl-phenylamine as a tan solid.

Preparation 3: 5-(4-Methoxy-phenoxy)-1H-indazole

5 A suspension of 4-(4-methoxy-phenoxy)-2-methyl-phenylamine (10 grams, 44 mmol) in 220 mL of water was treated with 14 mL of 12 M aqueous hydrochloric acid. After cooling to 0 °C, the mixture was treated dropwise with a solution of sodium nitrite (3.4 grams, 49 mmol) in 50 mL of water. The resulting solution was stirred for 20 minutes. The pH of the mixture was adjusted to 5 with 25% aqueous sodium acetate, and the mixture was then added 10 dropwise to a solution of *tert*-butyl thiol (5.1 mL, 4.1 grams, 45 mmol) in 100 mL of ethanol at 0 °C. After stirring for 30 minutes, the mixture was diluted with water and was extracted 3 times with diethylether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel eluting with 20% ethyl acetate-hexanes, affording 12 grams of an orange oil. A solution of the above 15 oil (12 grams, 36 mmol) in 210 mL of dimethyl sulfoxide was added dropwise to a mixture of potassium *tert*-butoxide (36 mmol) in 360 mL of dimethyl sulfoxide, and the resulting mixture was stirred for 24 hours at room temperature. The mixture was diluted with 1L of water and was extracted 3 times with ether and 2 times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was 20 triturated with *iso*-propylether, affording 7.3 grams of 5-(4-Methoxy-phenoxy)-1H-indazole as an orange solid. MS: 498.5 [M+H]⁺; 496.5 [M-H]⁻

Preparation 4: 5-(4-Methoxy-phenoxy)-1-pyridin-3-yl-1H-indazole

A mixture of 5-(4-methoxy-phenoxy)-1H-indazole (0.20 grams, 0.83 mmol) and 1.7 mL of anhydrous dimethyl sulfoxide (previously saturated with oxygen) was treated with 3-pyridylboronic acid (0.25 grams, 1.7 mmol), copper (II) acetate (0.23 grams, 1.2 mmol), 25 pyridine (0.34 mL, 0.33 grams, 4.2 mmol) and 4A molecular sieves (0.17 grams). After stirring for 14 days under an oxygen atmosphere, the mixture was diluted with water, extracted 3 times with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography 30 eluting with ethyl acetate-hexanes (0-100%), affording 5-(4-Methoxy-phenoxy)-1-pyridin-3-yl-1H-indazole (0.11 grams) (¹H NMR (CDCl₃, 400 MHz): δ 9.07 (d, 1H, J = 2.1 Hz), 8.60 (d, 1H, J = 4.2 Hz), 8.12 (s, 1H), 8.10 (dd, 1H, J = 1.3, 5.8 Hz), 7.65 (dd, 1H, J = 1.1, 9.6 Hz), 7.50 (dd, 1H, J = 5.0, 8.3 Hz), 7.25 (m, 2H), 7.00 – 6.80 (m, 5H), 3.80 (s, 3H) ppm) and 5-(4-Methoxy-phenoxy)-2-pyridin-3-yl-2H-indazole (0.050 grams) (¹H NMR (CDCl₃, 400 MHz): δ 35 9.12 (bs, 1H), 8.50 (b, 1H), 8.32 (d, 1H, J = 8.3 Hz), 8.29 (s, 1H), 7.73 (d\l d, 1H, J = 9.5 Hz), 7.54 (dd, 1H, J = 4.6, 7.9 Hz), 7.16 (dd, 1H, J = 2.1, 9.1 Hz), 7.01 (d, 2H, J = 9.1 Hz), 6.96 (s, 1H), 6.90 (d, 2H, J = 8.7 Hz), 3.81 (s, 3H) ppm) as colorless syrups.

Preparation 5: 4-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-phenol

A solution of 5-(4-Methoxy-phenoxy)-1-pyridin-3-yl-1H-indazole (0.11 grams, mmol) in 2 mL of methanesulfonic acid was treated with 0.2 grams of methionine. After stirring for 24 hours at room temperature, the mixture was treated with 1.2 grams of sodium hydroxide in 50 mL of water with cooling in an ice bath, neutralized with aqueous sodium bicarbonate, extracted 3 times with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*, affording 0.10 grams of 4-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-phenol as a colorless syrup. MS: 304.4 [M+H]⁺

Example 310 5-(2-Methoxy-ethyl)-5-[4-(2-pyridin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione

Ex. No.	Structure	MW	¹ H NMR (CD ₃ OD, 500 MHz)
3		487	δ 9.24 (bs, 1H), 8.78 (b, 1H), 8.62 (d, 1H, J = 4.7 Hz), 8.46 (d, 1H, J = 7.25 Hz), 7.73 (d, 1H, J = 8.8 Hz), 7.65 (dd, 1H, J = 4.7, 8.3 Hz), 7.16 (d, 1H, J = 9.8 Hz), 7.08 (s, 1H), 7.00 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.7 Hz), 3.60 (m, 2H), 3.27 (s, 3H), 2.56 (m, 2H) ppm.

A mixture of 4-(2-Pyridin-3-yl-2H-indazol-5-yloxy)-phenol (0.05 grams, 0.17 mmol), 2-methoxyethylbromobarbiturate (0.06 grams, 0.2 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (0.22 grams) and acetonitrile (1.5 mL) was shaken for 48 hours at room temperature. The mixture was treated with a solution of acetic acid in methanol (1:4 v/v), shaken for 20 minutes, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography eluting with an ethyl acetate-hexanes gradient (0-100% ethyl acetate). Trituration of the purified product with iso-propyl ether afforded 5-(2-Methoxy-ethyl)-5-[4-(2-pyridin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione (0.009 grams) as a colorless solid.

Preparation 1: 4-(2-Pyridin-3-yl-2H-indazol-5-yloxy)-phenol

A solution of 5-(4-methoxy-phenoxy)-2-pyridin-3-yl-2H-indazole (0.050 grams, mmol) in 1 mL of methanesulfonic acid was treated with 0.1 grams of methionine. After stirring for 24 hours at room temperature, the mixture was treated with 0.6 grams of sodium hydroxide in 25 mL of water with cooling in an ice bath, neutralized with aqueous sodium bicarbonate, extracted 3 times with ethyl acetate, and the combined organic layers were dried over sodium

sulfate, filtered and concentrated *in vacuo*, affording 0.05 grams of 4-(2-Pyridin-3-yl-2H-indazol-5-yloxy)-phenol as a colorless syrup. MS: 304.4 [M+H]⁺

Example 4

5-[{1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy}-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-

5

2,4,6-trione

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
4		504	505.8

A mixture of 4-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenol (0.20 grams, 0.625 mmol), 2-methoxyethylbromobarbiturate (0.18 grams, 0.60 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (0.40 grams) and acetonitrile (2 mL) was shaken for 24 hours at room temperature. The mixture was treated with a solution of acetic acid in methanol (1:4 v/v), shaken for 20 minutes, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography eluting with an ethyl acetate-hexanes gradient (0-100% ethyl acetate). Trituration of the purified product with *iso*-propyl ether afforded the title compound (0.079 grams) as a colorless solid. MS: 505.8 [M+H]⁺; 15 503.8 [M-H]⁻

Preparation 1: 1-(4-Fluoro-phenyl)-5-(4-methoxy-phenoxy)-1H-indazole

A mixture of 5-(4-methoxy-phenoxy)-1H-indazole (0.25 grams, 1.0 mmol), 4-fluorobromobenzene (0.23 mL, 0.36 grams, 2.08 mmol), cuprous oxide (0.15 grams, 1.0 mmol), potassium carbonate (0.29 grams, 2.08 mmol) and *N,N*-dimethylacetamide (0.25 mL) was stirred at 160 °C for 3 hours. After cooling to room temperature, the mixture was diluted with water, extracted 3 times with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with a gradient of ethyl acetate in hexanes (0-100%), affording 1-(4-Fluoro-phenyl)-5-(4-methoxy-phenoxy)-1H-indazole as a colorless solid. MS: 335.3 [M+H]⁺

25

Preparation 2: 4-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenol

A mixture of 1-(4-Fluoro-phenyl)-5-(4-methoxy-phenoxy)-1H-indazole (0.3 grams, mmol), methionine (0.40 grams, mmol) and 3 mL of methanesulfonic acid was shaken for 24 hours at room temperature. The mixture was treated with a solution of 1.8 grams of sodium hydroxide in 20 mL of water with cooling in an ice bath, and the aqueous phase was extracted

3 times with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*, affording 0.20 grams of 4-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenol as a colorless solid. MS: 321.7 [M+H]⁺

Example 5

5 **5-[4-(1-Isopropyl-1H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione**

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
5		452	453.6

A mixture of 4-(1-Isopropyl-1H-indazol-5-yloxy)-phenol (0.090 grams, 0.34 mmol), 2-methoxyethylbromobarbiturate (0.10 grams, 0.4 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (0.44 grams) and acetonitrile (2.3 mL) was shaken for 24 hours at room temperature. The mixture was treated with a solution of acetic acid in methanol (1:4 v/v), shaken for 20 min, and was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by radial chromatography eluting with 3:2 ethyl acetate-hexanes. Trituration of the purified product with *iso*-propyl ether afforded the title compound (0.075 grams) as a colorless solid. MS: 453.6 [M+H]⁺; 451.5 [M-H]⁻

Preparation 1: 1-Isopropyl-5-(4-methoxy-phenoxy)-1H-indazole

To a solution of 5-(4-methoxy-phenoxy)-1H-indazole (0.20 grams, 0.83 mmol) in 1 mL of dimethylformamide was added sodium hydride (0.040 grams of a 60% dispersion in mineral oil, 1.0 mmol). After shaking at room temperature for 10 minutes, the mixture was treated with 2-iodopropane (0.090 mL, 0.15 grams, 0.9 mmol). The mixture was heated to 50 °C for 6 hours. After cooling to room temperature, the mixture was diluted with water and was extracted 3 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-30% ethyl acetate in hexanes, affording 1-isopropyl-5-(4-methoxy-phenoxy)-1H-indazole (90 miligrams) MS: 283.4 [M+H]⁺ and 2-isopropyl-5-(4-methoxy-phenoxy)-2H-indazole MS: 283.4 [M+H]⁺ (75 miligrams) as colorless syrup.

Preparation 2: 4-(1-Isopropyl-1H-indazol-5-yloxy)-phenol

A solution of 1-Isopropyl-5-(4-methoxy-phenoxy)-1H-indazole (0.090 grams, mmol) in 2 mL of methanesulfonic acid was treated with 0.15 grams of methionine. After stirring for 24 hours at room temperature, the mixture was treated with 1.2 grams of sodium hydroxide in 25

mL of water with cooling in an ice bath, neutralized with aqueous sodium bicarbonate, extracted 3 times with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*, affording 0.090 grams of 4-(1-isopropyl-1H-indazol-5-yloxy)-phenol as a colorless syrup. MS: 269.7 [M+H]⁺

5

Example 6

5-[4-(2-Isopropyl-2H-indazol-5-yloxy)-phenoxy]-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
6		452	453.6

A mixture of 4-(2-isopropyl-2H-indazol-5-yloxy)-phenol (0.070 grams, mmol), 2-methoxyethylbromobarbiturate (0.10 grams, 0.4 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (0.44 grams, times mmol) and acetonitrile (2.3 mL) was shaken for 24 hours at room temperature. The mixture was treated with a solution of acetic acid in methanol (1:4 v/v), shaken for 20 minutes, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by radial chromatography eluting with 3:2 ethyl acetate-hexanes.

15 Trituration of the purified product with iso-propyl ether afforded the title compound (0.058 grams) as a colorless solid. MS: 453.6 [M+H]⁺; 451.6 [M-H]⁻.

Preparation 1: 4-(2-Isopropyl-2H-indazol-5-yloxy)-phenol

A solution of 2-isopropyl-5-(4-methoxy-phenoxy)-2H-indazole (0.075 grams, mmol) in 2 mL of methanesulfonic acid was treated with 0.15 grams of methionine. After stirring for 24 hours at room temperature, the mixture was treated with 1.2 grams of sodium hydroxide in 25 mL of water with cooling in an ice bath, neutralized with aqueous sodium bicarbonate, extracted 3 times with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*, affording 0.070 grams of 4-(2-isopropyl-2H-indazol-5-yloxy)-phenol as a colorless syrup. MS: 269.7 [M+H]⁺

Example 7**4-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-2-yl)-benzonitrile**

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
7		511	512.7

5 A mixture of 4-[5-(4-Hydroxy-phenoxy)-indazol-2-yl]-benzonitrile (0.070 grams, 0.22 mmol), 2-methoxyethylbromobarbiturate (0.10 grams, 0.4 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene (0.44 grams) and acetonitrile (2.3 mL) was shaken for 24 hours at room temperature. The mixture was treated with a solution of acetic acid in methanol (1:4 v/v), shaken for 20 minutes, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by radial chromatography eluting with 3:2 ethyl acetate-hexanes. Trituration of the purified product with *iso*-propyl ether afforded 4-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-2-yl)-benzonitrile (0.027 grams) as a colorless solid. MS: 512.7 [M+H]⁺; 510.6 [M-H]⁻

Preparation 1: 4-[5-(4-Methoxy-phenoxy)-indazol-2-yl]-benzonitrile

15 To a solution of 5-(4-methoxy-phenoxy)-1*H*-indazole (0.20 grams, 0.83 mmol) in 1 mL of dimethylformamide was added sodium hydride (0.040 grams of a 60% dispersion in mineral oil, 1.0 mmol). After shaking at room temperature for 10 minutes, the mixture was treated with 4-fluorobenzonitrile (0.11 grams, 0.9 mmol). The mixture was heated to 50 °C for 6 hours. After cooling to room temperature, the mixture was diluted with water and was extracted 3 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-30% ethyl acetate in hexanes, affording 4-[5-(4-Methoxy-phenoxy)-indazol-1-yl]-benzonitrile (110 milligrams) MS: 342.4 [M+H]⁺ and 4-[5-(4-Methoxy-phenoxy)-indazol-2-yl]-benzonitrile (75 milligrams) MS: 342.4 [M+H]⁺ as colorless syrups.

Preparation 2: 4-[5-(4-Hydroxy-phenoxy)-indazol-2-yl]-benzonitrile

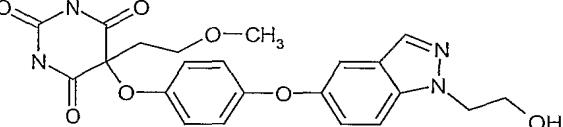
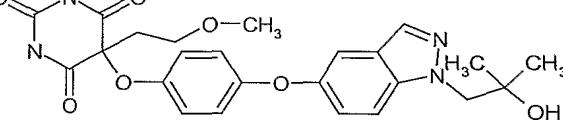
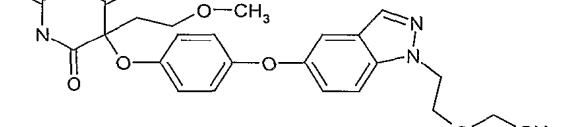
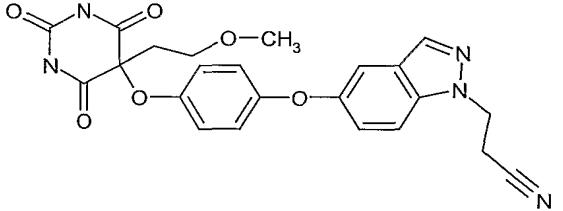
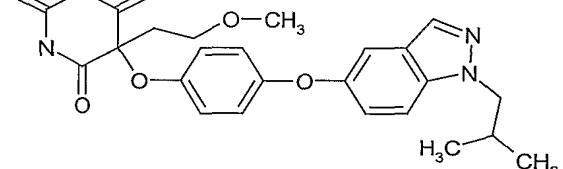
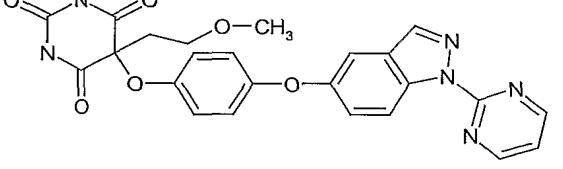
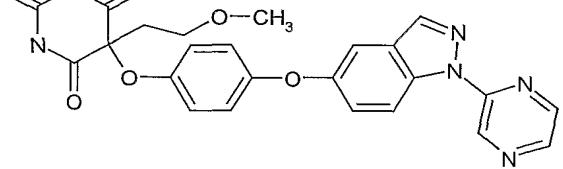
25 A solution of 4-[5-(4-Methoxy-phenoxy)-indazol-2-yl]-benzonitrile (0.075 grams, 0.22 mmol) in 1.6 mL of methylene chloride was treated with tetrabutylammonium iodide (0.13 grams, 0.36 mmol). After cooling to -78 °C, the mixture was treated dropwise with a solution of BCl_3 in methylene chloride (0.81 mL, 1 M, 0.81 mmol). After stirring for 20 minutes, the mixture was slowly warmed to room temperature and was stirred for 1 hour. The mixture was

cautiously neutralized with saturated aqueous sodium bicarbonate, and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*, affording 0.070 grams of 4-[5-(4-Hydroxy-phenoxy)-indazol-2-yl]-benzonitrile as a colorless solid. MS: 328.4 [M+H]⁺; 326.4 [M-H]⁻

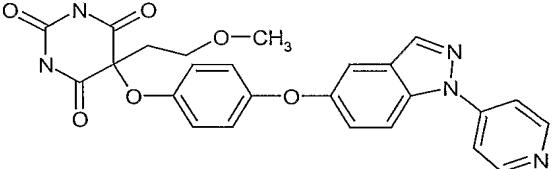
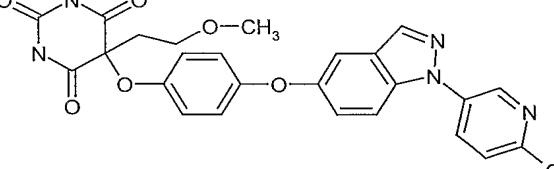
5 The following examples 8-22 were prepared according to methods analogous to that of Example 2, from the appropriate starting materials:

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
8		424.4	425.5
9		486.5	487.7
10		532.5	533.6
11		502.5	503.6
12		424.4	425.5
13		438.4	439.5

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Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
14		454.4	455.5
15		482.5	483.6
16		482.5	483.6
17		463.5	464.4
18		466.5	467.6
19		488.5	489.5
20		488.5	487.6[M-H] ⁻

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Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
21		487.5	489.1
22		521.9	522.3

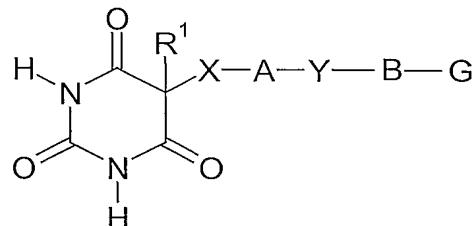
The following examples 23-31 were prepared according to methods analogous to that of Example 3, from the appropriate starting materials:

Example Number	Structure	MW	MS (APCI, m/z): [M+H] ⁺
23		487.5	488.6
24		486.5	487.6
25		424.4	425.5
26		438.4	439.6
27		482.5	483.7
28		482.5	483.6
29		466.5	467.6
30		488.5	489.6
31		521.9	522.3

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For 5 example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present 10 pharmaceutical carriers, as well as the type of formulation and mode of administration employed and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

We Claim:

1. A compound of the formula



I

wherein R¹ is selected from the group consisting of hydrogen, (R²)_{2n+1}-(C)_n- and (C₃-C₇)cycloalkyl; wherein said (C₃-C₇)cycloalkyl may be optionally substituted on any ring carbon atom able to support an additional substituent by one to two substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, R³-O-, perfluoro(C₁-C₄)alkoxy, R³-(C₁-C₄)alkyl-O-, R³-(C=O)-O-, (R³)₂N-(C=O)-O-, -NO₂, (R³)₂N-, R³-(C=O)-(NR⁴)-, R³-(SO₂)-(NR⁴)-, R³O-(C=O)-(NR⁴)-, (R³)₂N-(C=O)-(NR⁴)-, R³-S-, 10 R³-(S=O)-, R³-(SO₂)-, (R³)₂N-(SO₂)-, -CN, R³-(C=O)-, R³-O-(C=O)- and (R³)₂N-(C=O)-;

n is an integer from one to five;

each R² is independently selected from the group consisting of halo, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, R³-O-, perfluoro(C₁-C₄)alkoxy, R³-(C=O)-O-, (R³)₂N-(C=O)-O-, -NO₂, (R³)₂N-, R³-(SO₂)-(NR⁴)-, (R³)₂N-(C=O)-, R³-(C=O)-(NR⁴)-, R³O-(C=O)-(NR⁴)-, (R³)₂N-(C=O)-(NR⁴)-, R³-S-, 15 R³-(S=O)-, R³-(SO₂)-, (R³)₂N-(SO₂)-, -CN, R³-O-(C=O)-, and R³-(C=O)-;

wherein not more than three of said R² may be other than hydrogen and any one carbon atom of said -(C)_n- component of the R¹ can contain only one bond to a heteroatom;

wherein a carbon atom of any two R² may be taken together with the carbons to which they are attached to form a four to ten membered ring;

20 each R³ is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein each R³ may be optionally substituted on any carbon atom able to support an additional substituent by one to three substituents, wherein said substituents are independently selected from the group consisting of halo, hydroxy, amino, -CN, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂N-, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;

25 wherein each of said R³ (C₃-C₇)cycloalkyl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring;

wherein each of said R³ (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may be optionally 30 substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group consisting of (C₁-C₄)alkyl, (C₁-C₄)alkyl-(C=O)-, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;

R^4 is selected from the group consisting of hydrogen and (C_1 - C_4)alkyl;
 wherein said R^3 may be optionally taken together with said R^4 to form a three to eight membered ring;

X is selected from the group consisting of -O-, >C=O, -S-, >SO₂, >S=O, >NR⁵, -CH₂-,

5 -CH₂O-, -OCH₂-, -CH₂S-, -CH₂(S=O)-, -CH₂SO₂-, -SCH₂-, -(S=O)CH₂-, -SO₂CH₂-, -[N(R⁵)]CH₂-,
 -CH₂[N(R⁵)]-, -[N(R⁵)]SO₂- and -SO₂[N(R⁵)]-;

R^5 is selected from the group consisting of hydrogen and (C_1 - C_4)alkyl;

A is (C_6 - C_{10})aryl or (C_1 - C_{10})heteroaryl;

wherein said A (C_6 - C_{10})aryl or (C_1 - C_{10})heteroaryl may be optionally substituted on any

10 of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy and (C_3 - C_7)cycloalkyloxy;

Y is selected from the group consisting of a bond, -O-, -S-, >C=O, >SO₂, >S=O,

15 -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂SO-, -CH₂SO₂-, -SOCH₂-, -SO₂CH₂-, >NR⁶, -[N(R⁶)]CH₂-,
 -CH₂[N(R⁶)]-, -CH₂-, -CH=CH-, -C≡C-, -[N(R⁶)]-SO₂- and -SO₂[N(R⁶)]-;

R^6 is selected from the group consisting of hydrogen and (C_1 - C_4)alkyl;

B is a (C_1 - C_{10})heterocycl containing at least one nitrogen atom;

wherein one ring nitrogen atom of B is bonded to one carbon atom of G;

20 wherein said B may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, (C_3 - C_7)cycloalkyloxy, (C_6 - C_{10})aryl, (C_3 - C_7)cycloalkyl, (C_1 - C_{10})heteroaryl and (C_1 - C_{10})heterocycl;

25 G is (C_1 - C_6)alkyl or R^7 -(CR⁸R⁹)_p;

p is an integer from zero to four;

wherein said G (C_1 - C_6)alkyl may be optionally substituted by one to three substituents independently selected from F, Cl, Br, CN, OH, -(C=O)-OH, -(C=O)-O-(C_1 - C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1 - C_4)alkyl, -(C=O)-N[(C_1 - C_4)alkyl]₂, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, -NH₂, -NO₂, (C_1 - C_4)alkyl-NH-, [(C_1 - C_4)alkyl]₂-N- and (C_3 - C_7)cycloalkyloxy;

30 R^7 is selected from the group consisting of (C_3 - C_7)cycloalkyl, (C_6 - C_{10})aryl, (C_1 - C_{10})heteroaryl, and (C_1 - C_{10})heterocycl;

wherein each of said R^7 (C_6 - C_{10})aryl, (C_3 - C_7)cycloalkyl, (C_1 - C_{10})heteroaryl and (C_1 - C_{10})heterocycl may be optionally substituted on any of the ring carbon atoms capable of

35 supporting an additional substituent by one to three substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, (C_1 - C_4)alkoxy(C_1 - C_4)alkyl, -NH₂, -NO₂, (C_1 - C_4)alkyl-NH-, [(C_1 - C_4)alkyl]₂-N- and (C_3 - C_7)cycloalkyloxy;

(C_4) alkyl]₂-N-, (C_3-C_7) cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, and -(C=O)-N[(C_1-C_4)alkyl]₂;

wherein each of said R⁷ (C_3-C_7)cycloalkyl and (C_1-C_{10})heterocyclyl may be also optionally substituted on any of the ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring;

wherein each of said R⁷ (C_1-C_{10})heteroaryl and (C_1-C_{10})heterocyclyl may be optionally substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group consisting of (C_1-C_4)alkyl and (C_1-C_4)alkyl-(C=O)-;

each of R⁸ and R⁹ is independently selected from the group consisting of hydrogen and (C_1-C_4)alkyl;

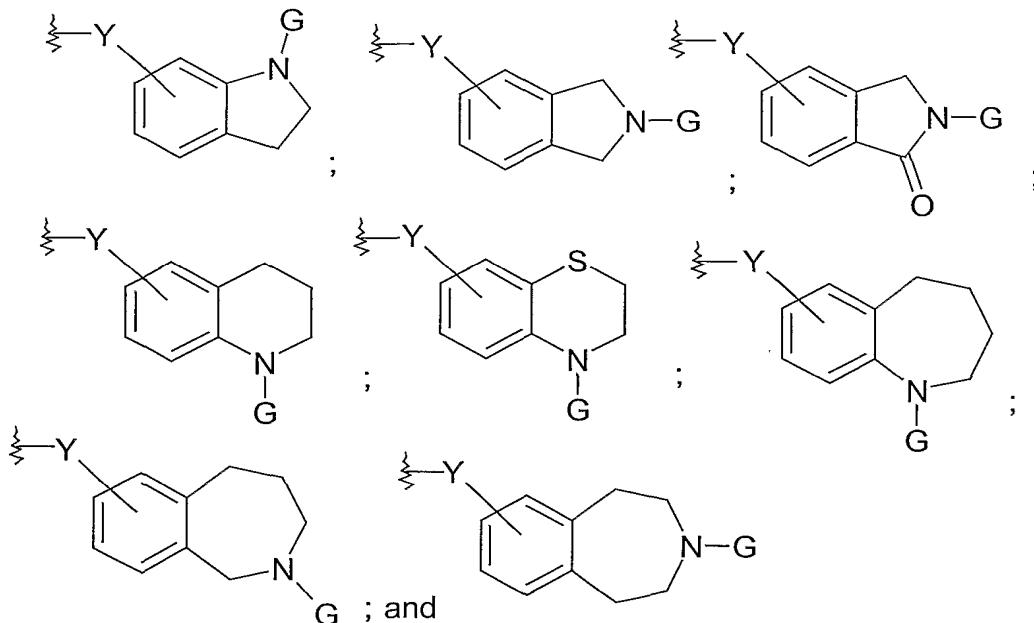
or R⁸ and R⁹ may be optionally taken together with the carbon to which they are attached to form a 3 to 8-membered carbocyclic ring;

with the proviso that the group -B-G is not methylazetidinyl or methylpiperidinyl; or a pharmaceutically acceptable salt thereof.

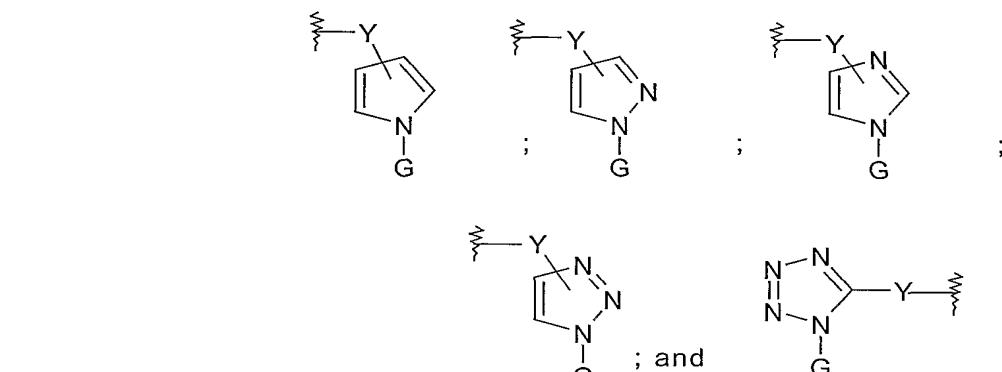
2. A compound according to claim 1, wherein B is a monocyclic saturated (5- to 7-membered)-heterocyclic ring containing at least one nitrogen atom; wherein said B may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_3-C_7)cycloalkyloxy, (C_6-C_{10})aryl, (C_3-C_7)cycloalkyl, (C_1-C_{10})heteroaryl and (C_1-C_{10})heterocyclyl; a monocyclic partially saturated (5- to 7-membered)-ring containing at least one nitrogen atom; wherein said B may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_3-C_7)cycloalkyloxy, (C_6-C_{10})aryl, (C_3-C_7)cycloalkyl, (C_1-C_{10})heteroaryl and (C_1-C_{10})heterocyclyl; a partially saturated (5- to 7-membered)-heterocyclic ring containing at least one nitrogen atom fused to an aromatic six membered ring; wherein said B may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_3-C_7)cycloalkyloxy, (C_6-C_{10})aryl, (C_3-C_7)cycloalkyl, (C_1-C_{10})heteroaryl and (C_1-C_{10})heterocyclyl; a monocyclic aromatic (5- to 6-membered)-heterocyclic ring containing at least one nitrogen atom; wherein said B may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_3-C_7)cycloalkyloxy, (C_6-C_{10})aryl, (C_3-C_7)cycloalkyl, (C_1-C_{10})heteroaryl and (C_1-C_{10})heterocyclyl; an aromatic (5- to 6-membered)-ring containing at least one nitrogen atom fused to an aromatic six membered ring; wherein said B may be optionally substituted on any of the ring carbon atoms capable of

supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₇)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

5 3. A compound according to any of the preceding claims wherein the group -Y-B-G has the formulae selected from the group consisting of

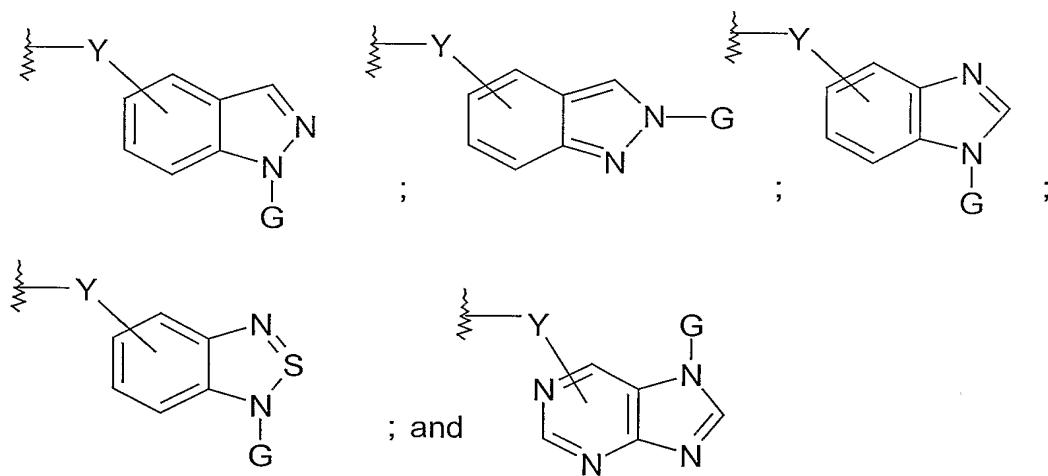


4. A compound according to any of the preceding claims wherein the group -Y-B-G has the formulae selected from the group consisting of



10

5. A compound according to any of the preceding claims wherein the group -Y-B-G has the formulae selected from the group consisting of



6. The compound according to claim 1, wherein said G is selected from (C_1-C_6)alkyl optionally substituted by one to three substituents independently selected from F, Cl, Br, CN, OH, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, -(C=O)-N[(C_1-C_4)alkyl]₂, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, -NH₂, -NO₂, (C_1-C_4)alkyl-NH-, [(C_1-C_4)alkyl]₂-N- and (C_3-C_7)cycloalkyloxy; -[R⁷-(CR⁸R⁹)_p]-, wherein p is zero; -[R⁷-(CR⁸R⁹)_p]-; wherein p is an integer from one to four; pyridinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NH₂, -NO₂, (C_1-C_4)alkyl-NH-, [(C_1-C_4)alkyl]₂-N-, (C_3-C_7)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, and -(C=O)-N[(C_1-C_4)alkyl]₂; pyridazinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NH₂, -NO₂, (C_1-C_4)alkyl-NH-, [(C_1-C_4)alkyl]₂-N-, (C_3-C_7)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, and -(C=O)-N[(C_1-C_4)alkyl]₂; pyrazinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NH₂, -NO₂, (C_1-C_4)alkyl-NH-, [(C_1-C_4)alkyl]₂-N-, (C_3-C_7)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, and -(C=O)-N[(C_1-C_4)alkyl]₂; phenyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C_1-C_4)alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_4)perfluoroalkoxy, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NH₂, -NO₂, (C_1-C_4)alkyl-NH-, [(C_1-C_4)alkyl]₂-N-, (C_3-C_7)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C_1-C_4)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C_1-C_4)alkyl, and -(C=O)-N[(C_1-C_4)alkyl]₂; and

NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂.

7. The compound according to any of the preceding claims wherein R⁷ is selected from (C₃-C₇)cycloalkyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂; and wherein said R⁷ (C₃-C₇)cycloalkyl may be optionally substituted on any ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring; (C₆-C₁₀)aryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂; (C₁-C₁₀)heteroaryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂; (C₁-C₁₀)heterocyclyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, -NO₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N-, (C₃-C₇)cycloalkyloxy, -(C=O)-OH, -(C=O)-O-(C₁-C₄)alkyl, -(C=O)-NH₂, -(C=O)-NH-(C₁-C₄)alkyl, and -(C=O)-N[(C₁-C₄)alkyl]₂; and wherein said (C₁-C₁₀)heterocyclyl may be optionally substituted on any ring carbon atoms capable of supporting two additional substituents with one to two oxo groups per ring.

8. The compound according to claim 1, wherein X is -O-.

9. A compound according to claim 1, wherein Y is -O-.

10. A compound according to any of the preceding claims wherein A is (C₆-C₁₀)aryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₇)cycloalkyloxy; or (C₁-C₁₀)heteroaryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br,

CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₇)cycloalkyloxy.

11. The compound according to any of the preceding claims wherein R¹ is (R²)_{2n+1}-(C)_n-, n is one or two;

5 each R² is independently selected from the group consisting of R³- and R³-O-; each R³ is independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl; wherein each R³ (C₁-C₄)alkyl may be optionally substituted by one to three substituents independently selected from the group consisting of (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

10 12. The compound according to any of the preceding claims wherein R¹ is (R²)_{2n+1}-(C)_n-, n is one or two; each R² is independently selected from the group consisting of R³- and R³-O-; wherein any four of said R³ are hydrogen and any one of said R³ is (C₁-C₄)alkyl; wherein each R³ (C₁-C₄)alkyl may be optionally substituted by one to three substituents independently selected from the group consisting of (C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl.

15 13. A compound according to claim 1, wherein said compound is selected from the group consisting of:

20 5-(2-Methoxy-ethyl)-5-[4-(1-pyridin-3-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

25 5-(2-Methoxy-ethyl)-5-[4-(2-pyridin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[1-(6-Chloro-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

30 5-(2-Methoxy-ethyl)-5-[4-(1-pyridazin-3-yl-1H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-[4-(2-pyridazin-3-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

35 5-(2-Methoxy-ethyl)-5-{4-[1-(6-methyl-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[2-(6-methyl-pyridin-3-yl)-2H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

40 5-(2-Methoxy-ethyl)-5-[4-(2-pyrimidin-4-yl-2H-indazol-5-yloxy)-phenoxy]-pyrimidine-2,4,6-trione;

5-{4-[2-(5-Fluoro-pyridin-2-yl)-2H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5-(2-Methoxy-ethyl)-5-{4-[1-(6-methoxy-pyridin-3-yl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione;

5-{4-[1-(3-Fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-5-(2-methoxy-ethyl)-pyrimidine-2,4,6-trione;

5 6-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-2-yl)-nicotinonitrile;

6-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-nicotinonitrile;

10 3-(5-{4-[5-(2-Methoxy-ethyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yloxy]-phenoxy}-indazol-1-yl)-benzonitrile; and

5-(2-Ethoxy-ethyl)-5-{4-[1-(4-fluoro-phenyl)-1H-indazol-5-yloxy]-phenoxy}-pyrimidine-2,4,6-trione; or

a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition for the treatment of a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

15. A method for treating a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, 25 gastric disorders, skin disorders and cancers in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/01546

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/515 C07D403/12 C07D403/14 A61P35/00

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 12611 A (BLAGG JULIAN ; PFIZER PROD INC (US)) 22 February 2001 (2001-02-22) cited in the application claims page 6, line 30 - page 7, line 28 ----- X CHIN, TEEN ET AL: "Molecular Recognition and Reactivity of Ruthenium(II) Bipyridine Barbituric Acid Guests in the Presence of Complementary Hosts: Ruthenium(II) Promoted Enolization of Barbituric Acids in Guest-Host Complexes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY (1997), 119(52), 12849-12858 CODEN: JACSAT; ISSN: 0002-7863, 1997, XP002248184 page 12851; examples G2, G3 ----- -/-	1-15 1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

17 July 2003

Date of mailing of the International search report

04/08/2003

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INTERNATIONAL SEARCH REPORT

International	ication No
PCT/IB us/01546	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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